The Journal of Pediatrics

VOL. 51 SEPTEMBER, 1957 No. 3

CONGENITAL SULFHEMOGLOBINEMIA

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IN THE past few years there has appeared in the literature many reports of congenital or familial methemoglobinemia. The case to be reported is a rare instance, perhaps the first, of a case of congenital and familial sulfhemoglobinemia.

CASE REPORT

S. O., No. 1599-754, a newborn female infant, was transferred to the Los Angeles County General Hospital, on August 19, 1955, at 3 days of age, weighing 5 pounds 5 ounces. Referring information stated that the baby had been cyanotic since birth and had required continuous oxygen therapy. The baby was one of fraternal triplets, the first having been stillborn, the second living and well, and the third, the patient. Labor had lasted for 30 hours. The baby breathed spontaneously, and no medication was used at birth. The mother had not taken any medication during her pregnancy.

On admission the baby appeared active, had a good cry, and was noticeably cyanotic. It was felt that the infant was in moderate respiratory distress. Examination of the ears, nose, throat, lungs, and heart disclosed no abnormality. No murmurs were heard, the heart rate was 100 to 110, and femoral pulses were felt. Initial study disclosed a hemoglobin of 19 grams per cent, and a white blood cell count of 43,000; chest x-ray was normal. A blood culture was taken. The baby was placed in an incubator and given daily injections of penicillin and streptomycin. It was the impression of the admitting doctor that the baby probably had congenital heart disease.

The day following admission the infant's color was unchanged, deeply cyanotic, but there was minimal respiratory distress. Feedings were started and the baby ate well. On the sixth day of life spinal and subdural taps gave negative results, repeat chest x-ray was normal, and examination disclosed clear lungs and no heart murmurs.

By the tenth day the baby appeared to be doing well, having no difficulty breathing and taking feedings well. The cyanosis, however, was unchanged. Because of the negative chest films and two negative blood cultures, antibiotics were discontinued and the baby was taken out of the incubator. On the seventeenth day the infant's weight had reached 6 pounds. Without supplementary oxygen, she had no respiratory effort or distress. Repeat x-rays of the chest were normal. An electrocardiogram was interpreted as showing possible right ventricular hypertrophy.

On the thirty-first day of life the baby weighed 7 pounds and was still

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cyanotic. The hemoglobin was 12.5 grams per cent and the white blood count was 18,000. It was at this time that the father offered the history of other "blue" members of the family. A sample of heparinized blood was taken from the baby. It was studied for abnormal blood pigments using the method of Evelyn and Malloy[1] which gave the following results:

Methemoglobin 0.2 gram per cent (normal less than 0.2 gram per cent)
Sulfhemoglobin 1.0 gram per cent (normal less than 0.2 gram per cent)

A repeat study of the blood yielded a value of 1.1 grams per cent sulfhemoglobin. At this time the family tree shown in Fig. 1 was obtained.

Other members of the family were not available for blood examination. The father's blood was examined and showed no methemoglobin and 1.4 grams per cent of sulfhemoglobin. He also appeared cyanotic. The baby was discharged on the forty-fifth day of life, weighing 7 pounds 4 ounces, and was still as cyanotic as on the day of admission.

When seen again at 6 months of age, with her twin sister, the baby had been well. The cyanosis was still prominent. A complete hemogram at this time was normal. The hemoglobin was 10.9 grams per cent, and the sulfhemoglobin was 1.03 grams per cent. Examination of the baby revealed no abnormalities. The baby had been developing normally and had not been ill since her discharge from the hospital.

DISCUSSION

As mentioned before, no case reports of congenital or familial sulfhemoglobinemia have been discovered in the literature. However, there are reported cases of this illness following the ingestion of certain drugs which lead to acquired sulfhemoglobinemia. The occurrence of congenital or familial methemoglobinemia was reported as early as 1844. Methemoglobinemia is also acquired as a result of the action of certain drugs or toxins.

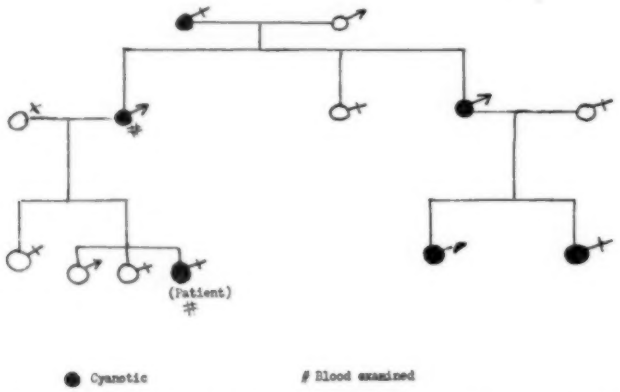

Fig. 1.—Family tree of the patient as related by the father. Only two members of the above family had spectrophotometric examination of their blood.

These pigments were reviewed by Finch,[2] in 1948. The power of these pigments in producing cyanosis is intense. Methemoglobin can be found in the red blood cell. Normally the cell has some of its hemoglobin iron oxidized to the ferric state of methemoglobin. This is an inert pigment, not capable of carrying oxygen. However, this abnormal pigment can be

reverted to the reduced ferrous state by ascorbic acid, methylene blue, and by reduction enzyme systems in the blood cell. Kravitz and associates[3] reported 0.1 to 0.5 gram per cent of methemoglobin as a normal finding in the red blood cell. Normally about 1 per cent of the total hemoglobin occurs as methemoglobin; constant activity of the cell's reduction enzymes keeps this level from going higher and causing noticeable cyanosis. In congenital methemoglobinemia there is believed to be a defect or absence of this reducing system, allowing as much as 20 to 40 per cent of the hemoglobin to remain in the oxidized form.[4-6]

Sulfhemoglobin is an inert pigment of unknown structure only present abnormally in the red blood cell. It is useless as an oxygen carrier. It is only known to occur as an acquired pigment after the ingestion of certain toxins or drugs. Unlike methemoglobin, however, once formed, the sulfhemoglobin cannot be reverted to hemoglobin. There is no known mechanism for its reconversion, and its disappearance from the blood is dependent upon the destruction or death of the red blood cell.[7] It is harmless except for its production of cyanosis and its anoxemic effect if large amounts are present. The interconversion of these pigments is shown in Fig. 2.

The recognition of these pigments is by spectrophotometric examination of the blood. Drawn blood of these patients is a chocolate color and does not turn red when shaken. Oxalated blood is centrifuged, diluted with water, and the absorption spectrum studied. The methemoglobin has its band at 630 mμ. Adding 5 per cent potassium cyanide removes the methemoglobin band and leaves the sulfhemoglobin band at 618 mμ. These pigments are intense in their capacity to produce cyanosis. Normally about 5 grams per cent of reduced hemoglobin causes noticeable cyanosis, whereas 1.5 grams per cent of methemoglobin and less than 0.5 gram per cent of sulfhemoglobin will produce comparable cyanotic color.[2]

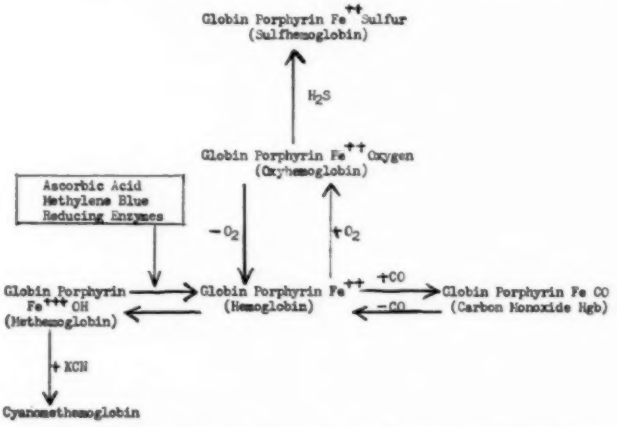

Fig. 2.—Interrelationships of the various pigments and hemoglobin. (From Cantaro, A., and Schepartz, B.: Biochemistry, W. B. Saunders Co.)

Methemoglobinemia is known to occur as an acquired disease after the ingestion of nitrites, aniline derivatives, pyridium, nitrophenol, sulfonamides, well water, crayons, and aromatic drugs.[2] It is also reported as a congenital and familial illness. Sulfhemoglobinemia is produced by the action of hydrogen sulfide on oxyhemoglobin, or after aromatic amines or sulfur is ingested in large amounts. Some drugs previously believed to cause methemoglobinemia have been found to actually produce sulfhemoglobinemia.[8, 9] The pigment has also been found in the blood after the production of hydrogen sulfide in the intestine by bacterial action, and its subsequent absorption. Unless potassium cyanide is used to differentiate the two pigments, sulfhemoglobinemia may go unrecognized and be diagnosed as methemoglobinemia.

Clinically, congenital methemoglobinemia may have a deep gray to cyanotic color manifest at birth. Mild respiratory distress with dyspnea may be present, and there may be a secondary polycythemia.[6] The degree of the symptoms will vary with the amount of methemoglobin and hence the lack of oxygen-carrying hemoglobin. Anoxic changes interfering with motor development have been reported.[10] With large and toxic amounts, death may occur. Sulfhemoglobinemia will also be symptomatic in proportion to the degree of abnormal pigment present. Methemoglobinemia can be reversed by ascorbic acid or by the intravenous injection of methylene blue. No known drug or mechanism is available for the reversal of sulfhemoglobinemia.

In the case described above, the mother had not taken any drugs during her pregnancy. There was no history of constipation or bowel disease in any member of the family. The cousins of this patient were also cyanotic in the newborn period and remained so two and three years later. At another hospital these children were diagnosed as having congenital methemoglobinemia. Perhaps the abnormal pigment in their blood was not differentiated by the method of Evelyn and Malloy, using potassium cyanide. All the affected relatives are reported by the father to be cyanotic. The baby described here therefore appears to represent an infant with congenital familial sulfhemoglobinemia.

SUMMARY

A case of a cyanotic newborn infant who had no cardiac, pulmonary, or neurological disease is described. This cyanosis proved to be due to the presence in the blood of an abnormal pigment, sulfhemoglobin. The nature, diagnosis, and symptomatology of methemoglobinemia and sulfhemoglobinemia are discussed. The infant described is a case of congenital familial sulfhemoglobinemia, never described before. The occurrence of abnormal pigments in the blood should be considered in any cyanotic newborn infant with no respiratory or cardiac findings.

I am grateful to Drs. J. Hodgman, R. F. Chinnock, I. Goldenberg for their assistance and encouragement in preparing this report. My thanks to Dr. A. Ware for his help with the laboratory studies.

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Of Quinsy and Swellyng of the Throte

The quinsy is a daungerous sickenes, both in young and olde, called in latin angina, it is an inflammacion of the necke with swelling & great pain, somtime it lieth in the very throte, upon the wesaunt pype, and than it is excedyng perylous, for it stoppeth the breath, and strangleth the pacient anone.

Otherwhyles it breaketh out lyke a bonche on the one side of the necke, and than also with very greate difficultie of breathynge, but it choketh not so sone as the first doeth, and it is more obedient to receyue curacion. The signes are apparaunt to syght, & besydes that the chylde can not crye, neyther swallow downe his meate & drinke without payne.

From Thomas Phaire: The Boke of Chyldren, 1544.

PAPER ELECTROPHORETIC STUDY OF SERUM PROTEINS IN CHILDREN WITH LEUKEMIA

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VARIOUS abnormalities in the composition of the serum proteins in patients suffering from leukemia have been reported. Hypoalbuminemia and increases in different globulin constituents have been observed.[1-6] The mechanisms by which the changes in the concentration of the various serum components occur are variable and not well understood. Tissue destruction, hemorrhage, fever, and infection may lead to increased concentrations of alpha and beta globulins.[7-10] High serum polysaccharide levels, which sometimes occur in leukemia,[11] may be related to the increased alpha$_2$ globulin level which has been frequently observed.[12-14] Gamma globulin may be increased in the presence of impaired hepatic function due to leukemic infiltration of the liver.

The present studies were undertaken to ascertain the changes in the serum protein pattern of children with leukemia during the course of their illness.

METHODS

Serum protein electrophoretic studies were performed on twenty-three patients with leukemia; seventeen cases were of the acute lymphocytic type; one, chronic lymphocytic; two, acute myelocytic; and three, chronic myelocytic. A total of 132 separate determinations were made in these twenty-three patients during the course of their disease.

Fasting blood samples were taken, and after clot retraction the serum was immediately separated by centrifugation. Total protein determinations and electrophoretic analyses were performed on the same day in which the samples were taken.

The standard biuret method[15] was used in determining the total serum protein. The serum sample was treated with biuret reagent, with which the serum proteins form a biuret complex. Total protein values were calculated from spectrophotometric readings obtained from a Coleman Junior Spectrophotometer set at a wave length of 540 mu and measured against a reagent blank set at 100 per cent transmission. The concentration of total proteins in the standard was obtained from a pooled sample of human sera and was determined by the micro-Kjeldahl method.[16]

The method used for paper electrophoretic analysis of the serum proteins followed closely that described

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This investigation was supported by the Alexander and Margaret Stewart Fund.

TABLE I. NORMAL VALUES FOR SERUM PROTEIN FRACTIONS*

AGE GROUPS	NO. OF CASES	TOTAL PROTEIN MEAN ± S.E.† (RANGE) ± 1.96 S.D.‡	TOTAL ALBUMIN MEAN ± S.E. (RANGE) ± 1.96 S.D.	TOTAL GLOBULIN MEAN ± S.E. (RANGE) ± 1.96 S.D.	ALPHA$_1$ GLOBULIN MEAN ± S.E. (RANGE) ± 1.96 S.D.	ALPHA$_2$ GLOBULIN MEAN ± S.E. (RANGE) ± 1.96 S.D.	BETA GLOBULIN MEAN ± S.E. (RANGE) ± 1.96 S.D.	GAMMA GLOBULIN MEAN ± S.E. (RANGE) ± 1.96 S.D.
		6.31 ± 0.131	3.44 ± 0.152	2.87 ± 0.179	0.30 ± 0.014	0.84 ± 0.089	1.02 ± 0.073	0.70 ± 0.054
5-6 mo.	11	(5.72 - 7.10)	(2.82 - 4.56)	(2.00 - 3.71)	(0.23 - 0.38)	(0.41 - 1.33)	(0.68 - 1.33)	(0.50 - 0.99)
		5.46 - 7.16	2.45 - 4.42	1.71 - 4.04	0.210 - 0.401	0.25 - 1.41	0.55 - 1.50	0.35 - 1.05
		6.68 ± 0.114	3.46 ± 0.120	3.20 ± 0.082	0.38 ± 0.0182	0.92 ± 0.033	1.07 ± 0.043	0.84 ± 0.040
7-11 mo.	15	(6.07 - 7.77)	(2.72 - 4.26)	(2.64 - 3.88)	(0.23 - 0.50)	(0.75 - 1.13)	(0.84 - 1.29)	(0.54 - 1.30)
		5.82 - 7.55	2.55 - 4.37	2.58 - 3.83	0.24 - 0.51	0.67 - 1.18	0.75 - 1.40	0.54 - 1.14
		6.92 ± 0.125	3.77 ± 0.117	3.15 ± 0.138	0.34 ± 0.014	0.86 ± 0.38	0.99 ± 0.048	0.95 ± 0.059
1-2 yr.	20	(5.73 - 7.80)	2.91 - 4.85)	(1.96 - 3.95)	(0.17 - 0.48)	(0.58 - 1.33)	(0.54 - 1.35)	(0.49 - 1.41)
		5.83 - 8.02	2.75 - 4.80	1.94 - 4.34	0.21 - 0.47	0.53 - 1.20	0.57 - 1.41	0.43 - 1.47
		7.11 ± 0.083	3.60 ± 0.099	3.48 ± 0.096	0.35 ± 0.019	0.91 ± 0.043	1.07 ± 0.048	1.16 ± 0.054
3-5 yr.	18	(6.43 - 7.70)	(3.10 - 4.51)	(2.77 - 4.37)	(0.20 - 0.49)	(0.59 - 1.30)	(0.70 - 1.61)	(0.67 - 1.56)
		6.40 - 7.82	2.77 - 4.42	2.69 - 4.27	0.20 - 0.52	0.54 - 1.25	0.67 - 1.45	0.71 - 1.61
		7.35 ± 0.090	4.03 ± 0.079	3.32 ± 0.090	0.35 ± 0.017	0.80 ± 0.032	0.96 - 0.030	1.20 - 0.050
6-13 yr.	24	(6.74 - 8.19)	(3.45 - 4.98)	(2.38 - 4.39)	(0.16 - 0.53)	(0.48 - 1.06)	(0.59 - 1.34)	(0.75 - 1.68)
		6.48 - 8.21	3.28 - 4.78	2.45 - 4.18	0.18 - 0.52	0.50 - 1.11	0.65 - 1.27	0.72 - 1.68

*Computed from data of Oberman and associates.[19]

†S.E. = Standard error.

‡± 1.96 S.D. = Range of mean ± 1.96 standard deviations and represents calculated values occurring between the 2.5 and 97.5 percentiles (95 per cent confidence).

TABLE II. ESSENTIAL CLINICAL DATA CORRELATED WITH THE

PATIENT, COLOR AND SEX	AGE AT ONSET	DIAGNOSIS	DURATION OF DISEASE	STATUS OF DISEASE	THERAPY	SERUM	
						NUMBER OF DETERMINATIONS	TOTAL PROTEIN
D. T., W.M.	2 yr.	Acute lymphocytic leukemia	14 mo.	Remission	6-mercaptopurine	3	7.0-7.3
Do. T. W.F.	11 mo.	Acute lymphocytic leukemia	11 mo.	Remission	6-mercaptopurine	5	5.3-7.3
				Relapse	6-mercaptopurine Amethopterin Cortisone	3	7.4
W. H. W.M.	6 yr.	Acute lymphocytic leukemia	10 mo.	Relapse	6-mercaptopurine Cortisone Azaserine Amethopterin Triethylene melamine	8	6.0-7.4
C. B. N.M.	4 yr.	Acute lymphocytic leukemia	11 mo.	Remission	6-mercaptopurine	2	6.8
				Relapse	6-mercaptopurine Cortisone Triethylene thiophosphoramide	8	6.7-8.5
J. T. W.M.	7 yr.	Acute lymphocytic leukemia	2½ yr.	Remission Relapse	No therapy Cortisone 6-mercaptopurine	3 2	6.6-7.3 7.1-8.5
R. N. N.M.	7 yr.	Acute lymphocytic leukemia	7 mo.	Remission	6-mercaptopurine	3	6.0-7.5
				Relapse	6-mercaptopurine	6	5.6-6.6
M. K. W.F.	3 yr.	Acute lymphocytic leukemia	9 mo.	Remission Relapse	6-mercaptopurine 6-mercaptopurine Amethopterin Cortisone	2 7	7.7 5.8-7.0
J. N. W.F.	4 yr.	Acute lymphocytic leukemia	4 mo.	Remission Relapse	6-mercaptopurine 6-mercaptopurine	2 1	6.2-6.3 6.2
D. W. W.M.	5 yr.	Acute lymphocytic leukemia	3½ yr.	Relapse	6-mercaptopurine Amethopterin Azaserine Cortisone	16	6.0-8.2
A. K. W.F.	3½ yr.	Acute lymphocytic leukemia	15 mo.	Remission	6-mercaptopurine	8	6.8-8.5
				Relapse	6-mercaptopurine Amethopterin Cortisone	2	7.0-7.3
G. S. W.M.	16 mo.	Acute lymphocytic leukemia	10 mo.	Remission Relapse	6-mercaptopurine 6-mercaptopurine Amethopterin Cortisone	1 10	8.2 6.3-8.1
L. G. W.F.	8 mo.	Acute lymphocytic leukemia	3 wk.	Relapse	6-mercaptopurine	1	6.0
R. B. W.M.	16 mo.	Acute lymphocytic leukemia	6 mo.	Relapse	6-mercaptopurine	1	6.6
C. W. W.M.	4 yr.	Acute lymphocytic leukemia	1 mo.	Relapse	6-mercaptopurine Cortisone	1	7.4

SERUM PROTEIN FRACTIONS IN TWENTY-THREE CHILDREN WITH LEUKEMIA

PROTEIN CONSTITUENTS IN GM./100 ML.						
ALBUMIN	GLOBULIN	$ALPHA_1$ GLOBULIN	$ALPHA_2$ GLOBULIN	BETA GLOBULIN	GAMMA GLOBULIN	COMMENT
3.30-3.82	3.18-4.0	0.37-0.41	0.49-1.19	0.80-1.10	0.94-1.37	Slight increase in total globulin and $alpha_2$ fraction
2.57-4.17	2.18-3.84	0.20-0.42	0.78-1.60	0.53-0.91	0.42-1.03	Low total protein, albumin, beta and gamma globulins; high $alpha_2$ globulin
3.17-3.52	3.88-4.23	0.37-0.56	1.22-1.56	0.84-1.36	0.54-1.08	Low albumin; high total globulin, $alpha_1$, $alpha_2$, and beta globulins
3.00-4.47	2.54-3.15	0.27-0.48	0.80-1.22	0.73-1.03	0.49-0.89	Low albumin and gamma globulin; high $alpha_1$ and $alpha_2$ globulins
2.91-3.10	3.90-3.89	0.36-0.44	0.78-0.93	0.66-1.26	0.55-0.63	Low albumin, high beta and total globulins
3.32-4.39	3.02-4.11	0.37-0.71	0.59-0.95	0.79-1.18	0.68-1.72	High total protein, $alpha_1$, and gamma globulins
3.98-4.19	2.41-3.31	0.22-0.30	0.51-0.97	0.93-1.06	0.75-1.06	Normal protein fractions
3.93-5.22	3.17-3.28	0.37-0.40	0.85-0.87	1.06-1.20	0.81-0.96	High albumin
2.51-3.70	2.30-4.68	0.30-0.43	0.54-1.33	0.54-1.03	0.92-1.54	Low albumin and beta globulin; high and low values for total globulin
1.85-3.12	3.18-4.05	0.37-0.66	0.81-1.42	0.84-0.94	0.59-0.94	Low total protein, albumin, gamma globulin, and total globulin; high $alpha_1$, $alpha_2$, and beta globulins
3.96-4.21	3.49-3.74	0.31-0.46	1.03-1.05	0.88-1.13	0.87-1.50	Normal protein fractions
2.85-3.71	2.72-3.48	0.26-0.43	0.59-1.00	0.74-1.21	0.29-1.19	Low total protein, albumin, total globulin, and gamma globulin
3.02-3.56	2.64-3.28	0.33-0.40	0.90-1.04	0.55-0.84	0.72-1.15	Low albumin and total globulin
2.79	3.41	0.47	1.26	1.01	0.67	Low albumin
2.92-4.60	2.48-4.05	0.18-0.60	0.45-1.24	0.70-1.64	0.55-1.60	High total protein, $alpha_1$, and beta globulins; low albumin and gamma globulin; high and low values for $alpha_2$ globulin
3.03-4.74	2.82-3.77	0.29-0.50	0.57-1.21	0.61-1.49	0.65-1.39	Low albumin, $alpha_2$, beta, and gamma globulins; high alpha, globulin
3.38-3.68	3.62	0.41-0.42	0.88-1.38	0.76-1.13	1.07-1.19	High $alpha_2$ globulin
4.52	3.78	0.28	0.78	0.94	0.84	Normal protein fraction
3.03-5.23	2.02-4.38	0.14-0.52	0.67-1.24	0.58-1.36	0.37-1.95	High albumin and total globulins; low and high values for $alpha_1$ and gamma globulins
3.08	2.92	0.43	1.12	0.87	0.50	Low gamma globulin
2.96	3.64	0.39	1.18	0.97	0.37	High $alpha_2$ and low gamma globulins
4.31	3.09	0.33	0.94	0.89	0.93	High $alpha_2$ globulin

TABLE II—

PATIENT, COLOR AND SEX	AGE AT ONSET	DIAGNOSIS	DURATION OF DISEASE	STATUS OF DISEASE	THERAPY	SERUM	
						NUMBER OF DETERMINATIONS	TOTAL PROTEIN
D. O'D. W.F.	5 mo.	Acute lymphocytic leukemia	3 mo.	Relapse	6-mercaptopurine Cortisone	5	5.4-5.8
J. B. W.M.	6 yr.	Acute lymphocytic leukemia	3 mo.	Relapse	6-mercaptopurine Azaserine	3	6.7-8.5
C. W. N.F.	4 yr.	Acute lymphocytic leukemia	3 mo.	Relapse	6-mercaptopurine	3	8.1-8.9
J. H. W.M.	10 yr.	Acute myelocytic leukemia	2 mo.	Relapse	Cortisone	2	6.6-6.8
K. F. W.M.	18 mo.	Acute myelocytic leukemia	5 mo.	Relapse	Cortisone	4	6.0-7.5
J. C. W.M.	5 yr.	Chronic myelocytic leukemia	5 yr.	Remission Relapse	No therapy Irradiation P^{32} Myleran Colcemid	1 4	6.0 5.3-6.9
V. S. W.M.	13 mo.	Chronic myelocytic leukemia	4 yr.	Remission	No therapy	5	6.6-8.5
C. J. N.F.	7 yr.	Chronic myelocytic leukemia	2 yr.	Remission	No therapy	4	7.0-7.1
				Relapse	Irradiation	1	7.8
W. Y. W.M.	2 yr.	Chronic myelocytic leukemia	6 mo.	Relapse	Cortisone Irradiation	5	6.0-6.9

by Durrum,[17] but with some modification. A strip of No. 3 Whatman filter paper, 30 mm. wide, was saturated with 0.075 ionic strength Veronal buffer at pH 8.6 and placed in a Spinco Model R cell. An electric current was sent through this system for one-half hour, allowing saturation of the strip by capillarity and producing equilibrium in the system. At the end of this period, 0.01 ml. of fresh, nonhemolyzed serum was applied to the apex of the paper strip. A current of 12 ma. and 78 to 100 volts was then applied for seventeen hours. This causes the negatively or positively charged protein particles to migrate toward the opposite pole. Since each protein fraction has a different mobility, the serum proteins separate into well-defined bands. The strip was dried at 110° to 120° C. for thirty minutes and stained overnight in Spinco dye B-1. It was then rinsed three times in 2.5 per cent acetic acid for ten minutes each time and finally dipped for five minutes in a solution of 2 per cent sodium acetate in 10 per cent acetic acid. Following this procedure the strip was blotted dry and further dried for one-half hour at 100° C. The intensity of color of each of the bands gauges the concentration of each individual protein fraction. The paper strip was then placed in a Spinco Analytrol densitometer, which converts the colored bands to graphic form. The area under each peak was determined from the integration record of the Spinco Analytrol and these values were converted

CONT'D

PROTEIN CONSTITUENTS IN GM./100 ML.						
ALBUMIN	GLOBULIN	ALPHA$_1$ GLOBULIN	ALPHA$_2$ GLOBULIN	BETA GLOBULIN	GAMMA GLOBULIN	COMMENT
2.35-3.68	1.72-3.35	0.26-0.68	0.41-1.13	0.49-1.72	0.24-1.02	Low albumin, alpha$_2$, and total globulins; high alpha$_1$. Low and high values for beta and gamma globulins
3.02-5.26	3.14-3.68	0.35-0.41	0.84-1.04	0.55-1.09	0.93-1.28	High and low values for albumin; low beta globulin
3.89-4.28	3.82-4.78	0.39-0.51	0.92-1.23	0.88-1.57	1.47-1.81	High alpha$_1$, beta, and total globulins
2.19-3.07	3.53-4.61	0.47-0.75	0.96-1.82	0.94	1.10-1.16	Low albumin; high alpha$_1$, alpha$_2$, and total globulins
3.54-3.96	2.46-3.72	0.23-0.52	0.69-1.31	0.94-1.12	0.44-1.46	High and low values for gamma globulins
2.90	3.10	0.39	0.80	0.67	1.23	Low albumin
2.45-3.54	2.77-3.58	0.35-0.53	0.59-1.07	0.43-0.68	0.82-1.22	Low total protein, albumin, and beta globulin; high alpha$_2$ globulin
3.22-5.12	2.63-3.61	0.17-0.44	0.60-0.85	0.66-1.18	1.02-1.42	High albumin and gamma globulin
2.72-4.08	3.02-4.28	0.16-1.50	0.50-1.21	0.53-1.22	1.04-1.63	Low albumin and beta globulin; high alpha$_1$ and alpha$_2$ globulins
3.62	4.18	0.46	1.00	1.03	1.69	High gamma globulin
2.97-3.45	3.03-3.45	0.32-0.47	0.84-1.09	0.92-0.98	0.79-1.26	Normal protein fractions

to a percentage of the total. Duplicate graphs were made and the percentages averaged to give as reliable a value as possible. Absolute values for each serum protein constituent were obtained from multiplication of each individual protein value by the calculated percentage of these substances.

In order to estimate the relative accuracy of our methods, in several instances simultaneous fractionation of selected sera by the paper electrophoretic method and the classical moving boundary method of Tiselius and Flodin[18] were performed, the results of which compared closely. This comparison has previously been reported from our laboratory.[19] Normal values for the mean plus or minus (±) the standard error of the mean, the observed range, and the range for the mean plus or minus (±) 1.96 standard deviations for serum protein constituents in the age groups encountered in this study are shown in Table I. These values have been computed from the data of Oberman and co-workers.[19]

RESULTS

In Table II are presented the essential clinical data and the serum protein electrophoretic findings in the twenty-three patients studied. The serum protein patterns were usually normal in most instances whether the patient was hematologically and clinically in remission or in relapse.

A decrease in the total protein occurred in ten instances and was present in six patients, one at the onset of the disease and five during the

terminal phase of illness; five patients had acute lymphocytic leukemia and one, chronic myelocytic leukemia. A slight increase in total protein concentration was present on two occasions. Hypoalbuminemia was observed in thirty specimens from ten patients (eight acute lymphocytic leukemias and two chronic myelocytic leukemias), two at the onset and eight during a period of relapse. Hyperalbuminemia was present in seven specimens from four different patients, three of whom were in remission. Alpha$_1$ globulin was high in twenty-two samples from eight patients with acute lymphocytic leukemia (6 of whom were in relapse), from one patient with acute myelocytic leukemia at the onset of the disease, and from one patient with chronic myelocytic leukemia during a remission. Low values for alpha$_1$ globulin were observed in one patient with acute lymphocytic leukemia in two instances during a partial remission. The concentration of alpha$_2$ globulin was increased in seven patients with acute lymphocytic leukemia, in sixteen specimens, fourteen of which were obtained during a relapse; and on one occasion in each of three patients, one with acute myelocytic leukemia and two with chronic myelocytic leukemia. A decreased value for alpha$_2$ globulin was observed in five samples from three patients with acute lymphocytic leukemia, in two instances the patient being in relapse and in three instances, in remission. Beta globulin concentrations were elevated in seven specimens from six patients with acute lymphocytic leukemia, and were decreased in ten samples, four obtained from two patients with chronic myelocytic leukemia, both in remission, and six from five patients with acute lymphocytic leukemia, three of whom were in relapse. Elevation of the gamma globulin concentration was present on one determination in each of three patients with acute lymphocytic leukemia, one while in remission and two in relapse; and in one instance in each of two patients with chronic myelocytic leukemia, one in remission and one in relapse. Decreased gamma globulin concentrations occurred twenty times in ten patients with acute lymphocytic leukemia, eight of whom were in relapse at the time of the determination; it was seen on one occasion in a patient with acute myelocytic leukemia in relapse. Total globulin concentrations over the range of normal were present in eight specimens from seven patients with acute lymphocytic leukemia, two of whom were in relapse; and in one patient with acute myelocytic leukemia at the onset of the disease. Low values for total globulins were observed in four specimens from as many patients, three of whom were in relapse.

Typical abnormal serum protein patterns in each of the four groups of leukemia are shown in Figs. 1 to 4. Variations from normal in the serum protein constituents in the children with acute lymphocytic leukemia consisted of a hypoalbuminemia, a decrease in gamma globulin, and less frequently an increase in alpha$_1$ and alpha$_2$ globulins. These changes occurred more often when the patient was in relapse; however, they were also at times observed during a complete hematological and clinical remission.

The one patient studied with chronic lymphocytic leukemia showed a consistently normal serum protein

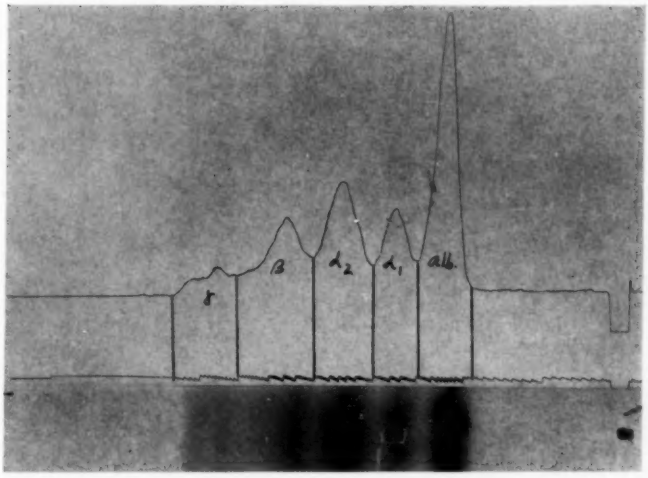

Fig. 1.—An abnormal paper electrophoretic pattern of the serum proteins in a patient with acute lymphocytic leukemia, showing low total albumin, high alpha$_1$ and alpha$_2$ and low gamma globulins. Above the paper strip is the corresponding pattern produced after analysis by the densitometer. The relative quantities of the given fractions are measured by calculating the area under each peak and relating this to the area under all the peaks.

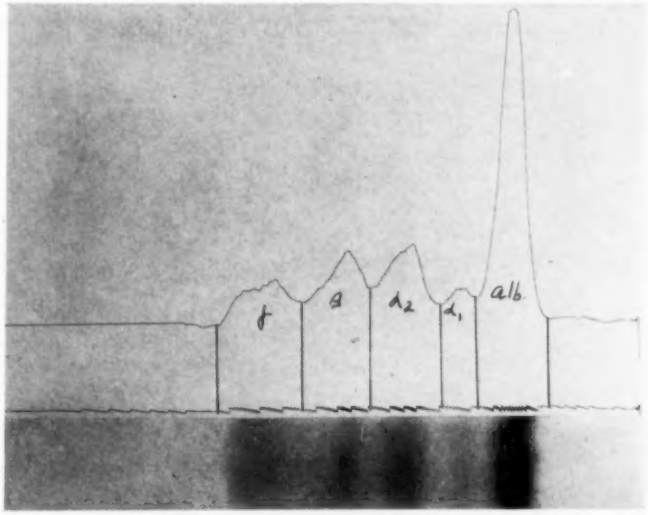

Fig. 2.—An abnormal paper electrophoretic pattern of the serum proteins in a patient with acute myelocytic leukemia, showing low total albumin and high alpha$_1$, alpha$_2$, and gamma globulins.

pattern which remained normal even during the terminal phase of the disease.

Of the two patients with acute myelocytic leukemia, one showed a decrease in albumin and an increase in both alpha$_1$ and alpha$_2$ globulin fractions.

The three patients with chronic myelocytic leukemia frequently showed

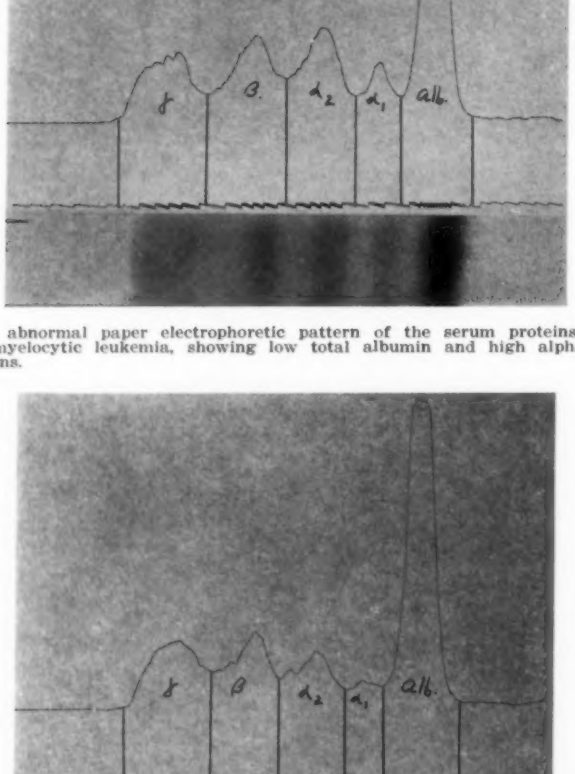

Fig. 3.—An abnormal paper electrophoretic pattern of the serum proteins in a patient with chronic myelocytic leukemia, showing low total albumin and high alpha$_1$, alpha$_2$ and gamma globulins.

Fig. 4.—A paper electrophoretic pattern of the serum proteins in a patient with chronic lymphocytic leukemia, showing normal serum protein fractions.

TABLE III. VALUES FOR THE SERUM PROTEIN FRACTIONS IN CHILDREN WITH LEUKEMIA

TYPE OF LEUKEMIA	NUMBER OF DETERMINATIONS	TOTAL PROTEIN GM./100 ML. MEAN ± S.E.* (RANGE) ± 1.96 S.D.†	TOTAL ALBUMIN GM./100 ML. MEAN ± S.E. (RANGE) ± 1.96 S.D.	TOTAL GLOBULIN GM./100 ML. MEAN ± S.E. (RANGE) ± 1.96 S.D.	ALPHA$_1$ GLOBULIN GM./100 ML. MEAN ± S.E. (RANGE) ± 1.96 S.D.	ALPHA$_2$ GLOBULIN GM./100 ML. MEAN ± S.E. (RANGE) ± 1.96 S.D.	BETA GLOBULIN GM./100 ML. MEAN ± S.E. (RANGE) ± 1.96 S.D.	GAMMA GLOBULIN GM./100 ML. MEAN ± S.E. (RANGE) ± 1.96 S.D.
Acute lymphocytic in relapse	77	6.97 ± 0.128 (5.4 – 8.9) 4.78 – 9.16	3.65 ± 0.134 (1.85 – 5.26) 1.39 – 5.91	3.33 ± 0.046 (1.72 – 4.78) 2.55 – 4.11	0.40 ± 0.018 (0.14 – 0.71) 0.08 – 0.71	0.95 ± 0.026 (0.41 – 1.42) 0.50 – 1.39	1.00 ± 0.026 (0.49 – 1.72) 0.62 – 1.35	0.93 ± 0.045 (0.24 – 1.95) 0.16 – 1.70
Acute lymphocytic in remission	29	6.99 ± 0.140 (5.3 – 8.5) 5.52 – 8.46	3.71 ± 0.104 (2.51 – 4.74) 2.63 – 4.79	3.31 ± 0.104 (2.18 – 4.68) 2.21 – 4.41	0.34 ± 0.391 (0.20 – 0.50) 0.07 – 0.75	0.90 ± 0.446 (0.49 – 1.60) 0.43 – 1.37	0.89 ± 0.428 (0.53 – 1.49) 0.44 – 1.34	0.96 ± 0.056 (0.42 – 1.54) 0.37 – 1.55
Acute myelocytic	6	6.75 ± 0.416 (6.0 – 7.5) 4.75 – 8.75	3.36 ± 0.265 (2.19 – 3.96) 2.09 – 4.63	3.39 ± 0.322 (2.46 – 4.61) 1.84 – 4.94	0.44 ± 0.076 (0.23 – 0.75) 0.07 – 0.81	1.07 ± 0.171 (0.69 – 1.82) 0.25 – 1.89	0.99 ± 0.018 (0.94 – 1.12) 0.90 – 1.08	0.88 ± 0.167 (0.44 – 1.46) 0.08 – 1.67
Chronic myelocytic in relapse	5	6.5 ± 0.423 (5.3 – 7.8) 4.66 – 8.34	3.23 ± 0.206 (2.45 – 3.62) 2.33 – 4.13	3.27 ± 0.219 (2.77 – 4.18) 2.31 – 4.23	0.42 ± 0.034 (0.35 – 0.53) 0.27 – 0.57	0.83 ± 0.098 (0.59 – 1.07) 0.40 – 1.26	0.65 ± 0.103 (0.43 – 1.03) 0.30 – 1.00	1.17 ± 0.359 (0.82 – 1.69) 0.35 – 2.69
Chronic lymphocytic	5	6.38 ± 0.148 (6.0 – 6.9) 5.73 – 7.03	3.09 ± 0.464 (2.97 – 3.45) 1.07 – 5.11	3.29 ± 0.083 (3.03 – 3.45) 2.94 – 3.64	0.39 ± 0.032 (0.32 – 0.47) 0.25 – 0.53	1.00 ± 0.054 (0.84 ± 1.09) 0.76 – 1.24	0.88 ± 0.011 (0.92 – 0.98) 0.83 – 0.93	1.01 ± 0.088 (0.63 – 1.26) 0.63 – 1.39

*S.E. = Standard error.
†± 1.96 S.D. = Range of mean ± 1.96 standard deviations and represents calculated values occurring between the 2.5 and 97.5 percentiles (95 per cent confidence).

a low albumin and occasionally an increase in alpha$_2$, and decrease in beta, globulins. These changes were observed both when the patient was in remission and when in relapse.

In order to ascertain the statistical reliability of these determinations, the kemia studied, both during remission and during relapse (Table III). All leukemia patients studied fell within the age range of 5 months to 13 years and were grouped according to type and stage of the disease, irrespective of age. In Figs. 5 to 11 the values

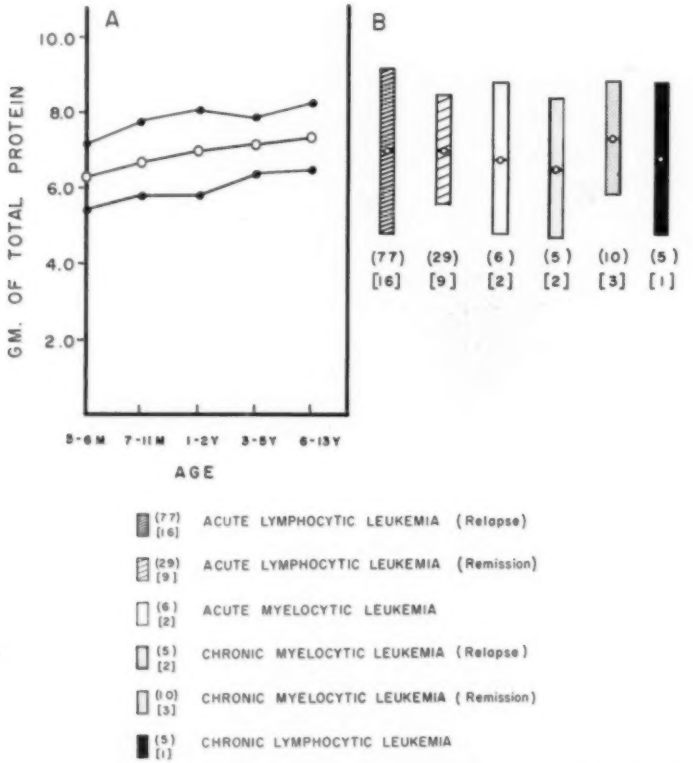

Fig. 5.—*A* is a plot of the total serum protein as a function of age (computed from data of Oberman and co-workers). ——O—— = the arithmetic mean; ——•—— = the mean ± 1.96 standard deviations of the mean. *B* compares the total serum protein values of the several types of leukemia. The ordinate dimensions are identical with those of *A*. ( ) = number of determinations; [ ] = number of patients. The mid-point of the bar indicates the arithmetic mean and the extreme points represent the mean ± 1.96 standard deviations of the mean.

mean plus or minus (±) the standard error of the mean, the observed range, and the range for the mean plus or minus (±) 1.96 standard deviations of the mean were computed in each of the four groups of patients with leu- for the mean plus or minus (±) 1.96 standard deviations of the mean for each serum protein fraction in leukemia patients are compared with the normal values. The values of 95 per cent should fall within this range and

they represent values occurring between the 2.5 and 97.5 percentiles. This assumes, however, that the distribution of the values is symmetrical, having an even scattering with 2.5 per cent at each end of the curve. In three instances, however, minus 1.96 standard deviations of the mean fell below the zero level (alpha$_1$ values for acute lymphocytic leukemia in remission and chronic myelocytic leukemia in remission, and gamma globulin values for chronic myelocytic leukemia in remission, and gamma globulin

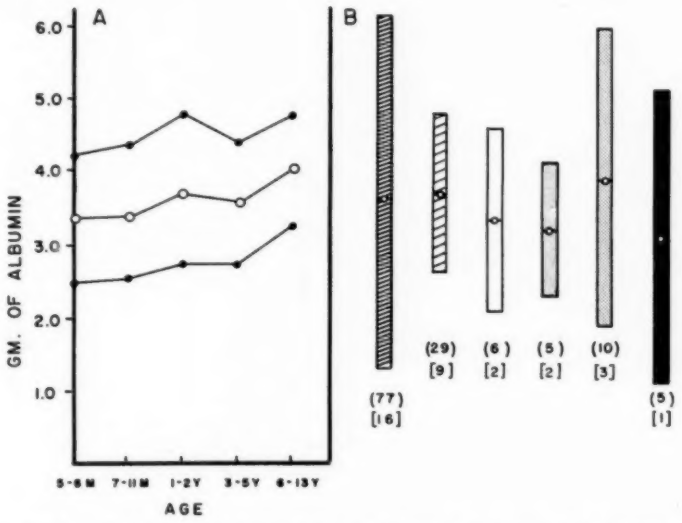

Fig. 6.—*A* and *B* compare the total serum albumin values in normal and leukemic patients. Specificities of legend as in Fig. 5.

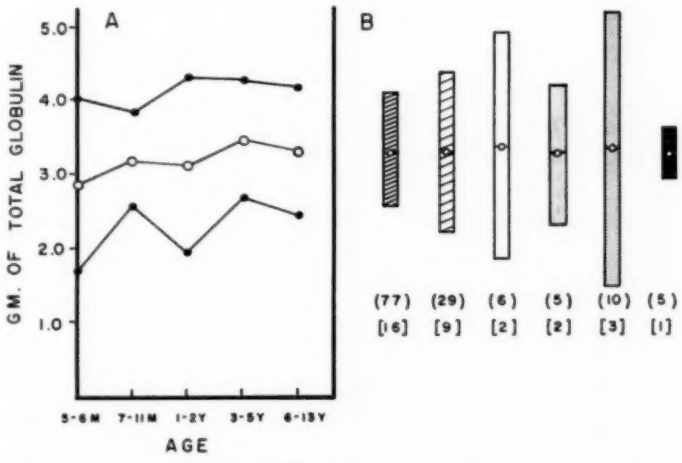

Fig. 7.—*A* and *B* compare the total serum globulin values in normal and leukemic patients. Specificities of legend as in Fig. 5.

seen in these instances that 2.5 to 5.0 per cent are in the highest range values. However, this may be a reflection of the relatively small number of determinations in these instances. As can be seen from Figs. 5 to 11, the mean values in each group of leukemia patients studied fell within the normal range for the specific age groups encountered. The range for the mean plus or minus (±) 1.96 standard deviations of the mean was, however, in most instances well beyond the normal limits.

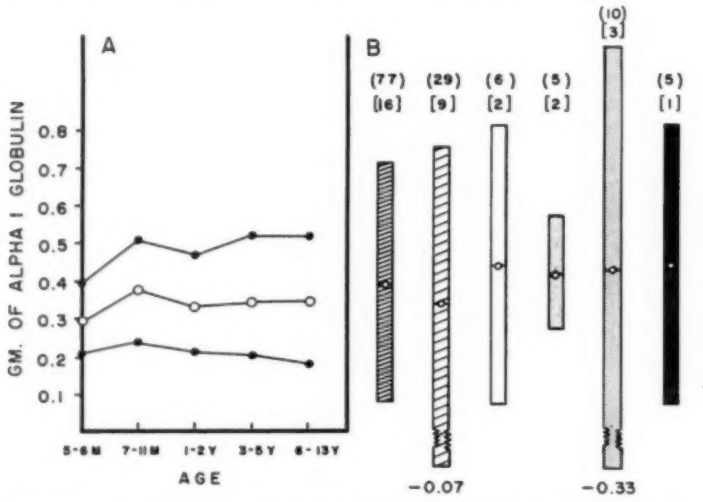

Fig. 8.—*A* and *B* compare the alpha$_1$ globulin values in normal and leukemic patients. Specificities of legend as in Fig. 5.

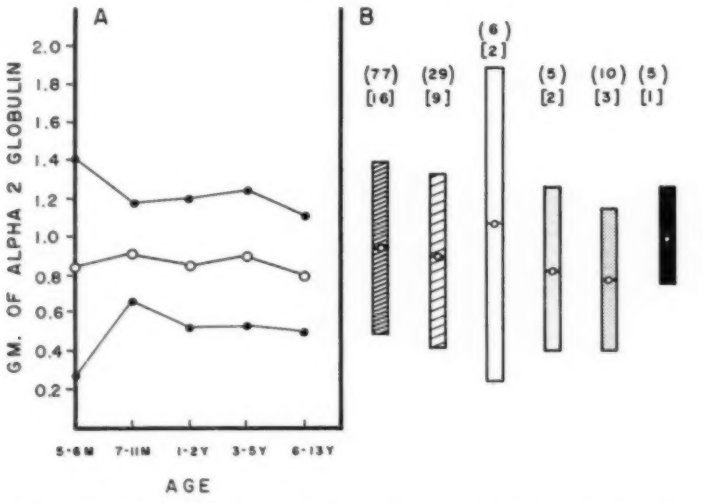

Fig. 9.—*A* and *B* compare the alpha$_2$ globulin values in normal and leukemic patients. Specificities of legend as in Fig. 5.

Wide variations in the serum protein fractions in children with leukemia can therefore be predicted. From the present study, this is particularly evident in the albumin fraction of patients with acute lymphocytic leukemia in relapse or chronic myelocytic leukemia in remission, in the total globulin fraction of patients with acute myelocytic leukemia in remission, in the alpha$_1$ globulin fraction of all leukemia patients except those with chronic myelogenous leukemia in remission, in the alpha$_2$ fraction of those patients with acute myelocytic leukemia, and in the gamma globulin

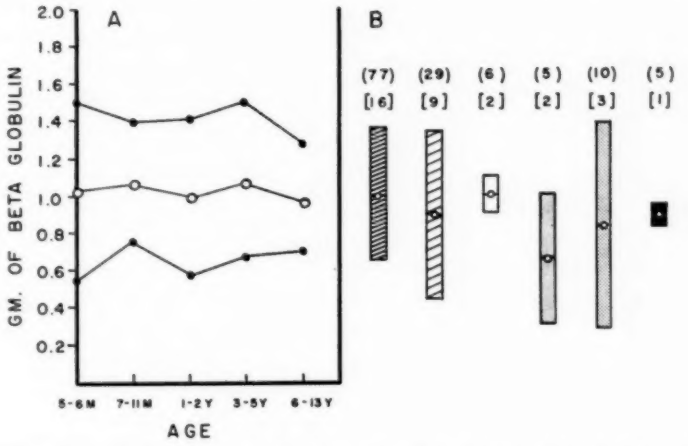

Fig. 10.—*A* and *B* compare the beta globulin values in normal and leukemic patients. Specificities of legend as in Fig. 5.

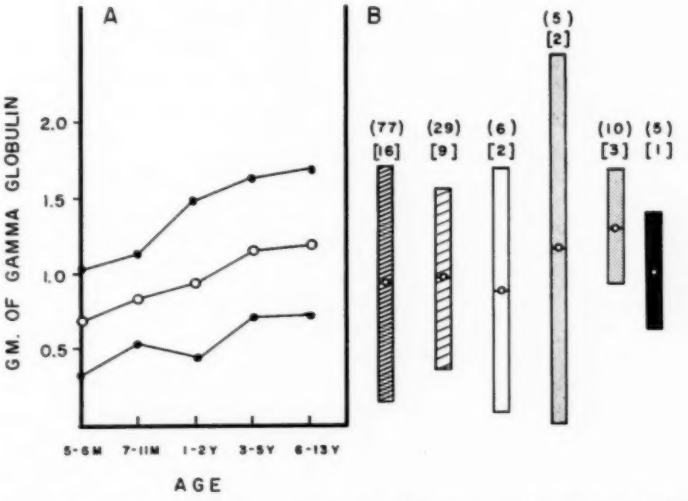

Fig. 11.—*A* and *B* compare the gamma globulin values in normal and leukemic patients. Specificities of legend as in Fig. 5.

fraction of patients with either acute lymphocytic or acute myelocytic leukemia in remission or relapse and in chronic myelocytic leukemia in relapse.

DISCUSSION

The results of the present study of the serum protein pattern in children with leukemia agree with the findings in previous reports of adult leukemia. The serum proteins may either have a normal electrophoretic composition or show alterations of a nonspecific nature. Hypoproteinemia was observed in patients only during the acute phase of their disease and therefore would appear to be related to tissue destruction. Hypoalbuminemia and increases in the different globulin components were more consistently observed in patients with acute leukemia, as has been previously reported.[1-6] The degree to which these changes occur is usually proportional to the severity and progression of the disease[6]; Gómez and Mora,[20] however, in their patients could find no correlation between the changes in the electrophoretic serum protein pattern and the severity of the disease. Elevation of the gamma globulin fraction, which was present in three patients with acute lymphocytic leukemia and two with chronic myelocytic leukemia, may be related to leukemia infiltration of the liver or to abnormal components having the same electrophoretic mobility as gamma globulin. Rundles and associates[6] found abnormal protein constituents in six patients with leukemia. This anomalous component was seen between the beta and gamma fractions. Cryoglobulins which appear with the gamma globulin fraction electrophoretically have been observed in several patients with subleukemic lymphatic leukemia[21-24] and in three patients with chronic lymphocytic leukemia.[25-27] The serum proteins in patients with chronic lymphocytic leukemia are usually normal,[1-4] as was observed in the one case included in the present study.

There did not appear to be any direct correlation between the alteration of serum protein constituents and the chemotherapeutic drugs employed in the therapy of these patients, except in the production of a hematological and clinical remission with a consequent reversal of the serum proteins to normal values in some instances. During the use of steroids there was sometimes observed a decrease in the albumin fraction; however, all patients in whom steroid therapy was used were in relapse.

Changes in the electrophoretic serum protein components appeared to be of little value in establishing a diagnosis of leukemia; however, the appearance of abnormal patterns or the presence of anomalous constituents may lead one to suspect progression of the disease.

SUMMARY

1. Serum protein analyses by paper electrophoresis on twenty-three children with leukemia have been presented.

2. Normal serum protein patterns were frequently observed. Variations from normal consisted of low albumin and gamma globulin and occasionally an increase in alpha$_1$ and alpha$_2$ globulins in patients with acute lymphocytic leukemia. In acute myelogenous leukemia a decrease in the

albumin fraction and an increase in alpha$_1$ and alpha$_2$ globulins occurred. A low albumin and beta globulin and occasional elevation of the alpha$_2$ globulin were sometimes seen in patients with chronic myelocytic leukemia. The one patient studied with chronic lymphocytic leukemia showed a normal serum protein pattern.

3. The mean values for each serum protein constituent in each group of leukemia patients studied fell within the normal range; however, wide variations from the mean plus or minus (±) 1.96 standard deviations of the mean were encountered.

4. No direct correlation could be made between the alteration of serum protein constituents and the drugs employed in the therapy of these patients except for a decrease in the albumin fraction during steroid therapy.

5. Alterations in the normal serum protein fractions in patients with leukemia is probably of a nonspecific nature and may be related to tissue destruction, fever, or infection.

6. Changes in the electrophoretic serum protein components in the present study were of little value in the diagnosis of leukemia; however, the presence of abnormal patterns may lead one to suspect a relapse and progression of the disease.

We acknowledge the helpful advice of Miss Mary Wilkinson of the National Institutes of Health for the statistical evaluation of these data.

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June 23, 1779. Charles Bagge broke out with small-pox. Few children are left who can be counted well, and they are very anxious to have small-pox, and visit the sick gladly. . . . June 30 Little Betsy Bagge, who has often wept because she was the only little girl who did not have small-pox, has now taken it . . . August 17. All of the little girls, and all of the little boys except Johannes Stockberger, have fully recovered from small-pox, and without any permant injury.

A. L. FRIES: RECORDS OF THE MORAVIANS IN NORTH CAROLINA, RALEIGH, N. C., 1312.

STEROID THERAPY FOR RHEUMATIC FEVER

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RICHMOND, VA.

PURPOSE

IN SPITE of several years of careful and well-planned research, the value of the addition of steroid drugs to the therapeutic armamentarium of rheumatic fever is not clearly defined. This study presents the results of the treatment of ninety-four patients with active rheumatic fever with varying doses of cortisone orally at the Medical College of Virginia Hospitals since 1950. With a drug of this kind and a disease as naturally variable as rheumatic fever, it is difficult to clinically assess and make valid comparisons. The facts will be presented with the hope that their addition to other clinical studies may help clarify this problem.

MATERIALS AND METHODS

All patients studied were hospitalized at the Medical College of Virginia Hospitals and completely studied before, during, and after the drug was used. Only those who met the modified Jones criteria for the diagnosis of rheumatic fever[1] were included. Complete diagnostic studies for rheumatic fever, as well as blood electrolytes and blood cultures, were done prior to any such therapy. Blood electrolytes, sedimentation rates, and C-reactive protein tests, in addition to complete blood counts and urinalyses, were repeated at frequent intervals during and after therapy. Changes in heart size were evaluated by a six-foot roentgenogram of the chest in inspiration, with measurements of cardio-thoracic ratios. Electrocardiograms were recorded at frequent intervals.

The ninety-four patients were divided, with forty-six white and forty-eight Negro (forty-three males and and fifty-one females). The ages varied from 4 to 18 years, with a mean of 10 years.

Four plans of therapy have been used (Table I).

Group I.—In 1950 the first cortisone became available. The dosage schedule was not fixed and the first twenty-four patients in the years 1950 through 1953 were given a maximum daily dose of 150 mg. of oral cortisone. Many patients received less than this. The drug was given for approximately three weeks. It was given parenterally only if vomiting precluded oral use.

The criteria for the need of the drug were not known and it was reserved for either the early cases or those with severe heart disease. Many patients were treated with aspirin alone and did not receive steroids. Only one case of chorea without heart disease was included in this group. There were ten who had the disease less than forty-two days when therapy was begun and fourteen who received it later in their illness. Of the latter fourteen, ten had either pericarditis, failure, or both.

Group II.—In 1954, a more carefully planned schedule was begun. A daily oral dose of 200 mg. for the first fourteen days and tapered over a

From the Department of Pediatrics, Medical College of Virginia, and the Virginia State Health Department.

sixty-one-day period was instituted (Table II). In the past three years forty-five patients have been so treated. During 1954 and part of 1955 this program was started on all pediatric cases admitted who had a definite diagnosis of active rheumatic fever of less than forty-two days' duration with or without heart involvement. It was also used on long-standing cases if they appeared critically ill. Seven of the twelve patients ill over forty-two days at the onset of the drug therapy had either pericarditis, failure, or both.

During the last year many patients with only joint involvement or chorea as a major manifestation have not received cortisone and were therefore excluded from this study. Only those with carditis have been so treated. All patients with carditis were given steroids if their duration was under forty-two days.

Group III.—In late 1955 reports to the effect that even larger doses were more protective occasioned a new schedule with a maximum daily dose of 300 mg. of cortisone daily for twenty-one days, which was then tapered over a sixty-one-day period (Table III). The next seventeen patients with the same diagnostic criteria were so treated. Fourteen had been ill less than forty-two days and only three were of longer duration. Two of the latter had cardiac failure when therapy was begun.

Group IV.—A final group of eight patients have been treated with prednisone. Six of the eight patients had either pericarditis or failure. These are recently treated patients and only very ill ones were included, since the drug was not available through the usual channels. If failure was prominent it was hoped that this would

TABLE I. DOSAGE SCHEDULES

GROUP	YEAR	CORTISONE DOSAGE MAXIMUM PER DAY	NO. PATIENTS
I	1950-1953	150 mg., tapered for about 21 days	24
II	1954-early 1955 and late 1956	200 mg. daily for 14 days—total of 61 days	45
III	Late 1955 and early 1956	300 mg. daily for 21 days—total of 61 days	17
IV	1955-1956	Prednisone 60 mg. daily for 21 days—total of 61 days	8

TABLE II. CORTISONE THERAPY IN TREATMENT OF RHEUMATIC FEVER WITH ACTIVE CARDITIS—200 MG. SCHEDULE

Chart No. ---------- Sex ----------
Name ---------- Age ----------

DATE	DAY NO.	CORTISONE DAILY DOSE	DATE	DAY NO.	CORTISONE DAILY DOSE
	1	200 mg.		41	100 mg.
	14	200 mg.		47	100 mg.
	15	187½ mg.		48	87½ mg.
	16	187½ mg.		49	87½ mg.
	17	175 mg.		50	75 mg.
	18	175 mg.		51	75 mg.
	19	162½ mg.		52	62½ mg.
	20	162½ mg.		53	62½ mg.
	21	150 mg.		54	50 mg.
	34	150 mg.		55	50 mg.
	35	137½ mg.		56	37½ mg.
	36	137½ mg.		57	37½ mg.
	37	125 mg.		58	25 mg.
	38	125 mg.		59	25 mg., 80 mg. Acthar gel
	39	112½ mg.		60	12½ mg., 80 mg. Acthar gel
	40	112½ mg.		61	12½ mg., 80 mg. Acthar gel

lead to less fluid retention. The dosage was 60 mg. per day, tapered over a sixty-one-day period for all but one small child who received a maximum dose of 40 mg. daily over the same period. In several cases a longer period of therapy was individually ordered as was deemed necessary.

pericarditis or failure when the drug was started. As noted in Table IV, five, or 20.8 per cent, died.

Another 20.8 per cent had essentially unchanged hearts as regards size and murmur. Further progression of the murmur or heart enlargement was found in 12.5 per cent. Only

TABLE III. CORTISONE THERAPY IN TREATMENT OF RHEUMATIC FEVER WITH ACTIVE CARDITIS—300 MG. SCHEDULE

Chart No. ---------- Sex ----------
Name ---------- Age ----------

DATE	DAY NO.	CORTISONE DAILY DOSE	DATE	DAY NO.	CORTISONE DAILY DOSE
	1	300 mg.		51	75 mg.
	21	300 mg.		52	50 mg.
	22	200 mg., 80 mg. Acthar gel		54	50 mg.
	23	200 mg., 80 mg. Acthar gel		55	37½ mg.
	35	200 mg.		57	37½ mg.
	36	150 mg.		58	25 mg.
	39	150 mg.		59	25 mg., 80 mg. Acthar gel
	40	100 mg., 80 mg. Acthar gel		60	25 mg., 80 mg. Acthar gel
	48	100 mg., 80 mg. Acthar gel		61	12½ mg., 80 mg. Acthar gel
	49	75 mg.			

TABLE IV. TWENTY-FOUR PATIENTS (GROUP I) GIVEN 150 MG. CORTISONE DAILY

	DAY THERAPY STARTED					
PRETREATMENT DIAGNOSIS	1-7	8-14	15-28	29-42	42-1 YR.	OVER 1 YR.
M. I.	1					
M. I. and C. E.	1	3	1*	1 (1)	(2) (2)*	
M. I., M. S., and C. E.					2 (1)*	(1)
A. I., M. V., and C. E.				1	1	(1) 1* (1)*
M. I. and M. S.			1			(1)*
No H. D.					1	
POSTTREATMENT DIAGNOSIS						
Murmur and size same				1	1	3
Less murmur, size same			1			
Same murmur, less C. E.		2		1	3	
No H. D.	1	1			2	
More murmur				1	1	
More murmur and C. E.	1					
Died			1		2	2

( ) = cardiac failure, * = pericarditis, M. I. = mitral insufficiency, M. V. = mitral valve disease, M. S. = mitral stenosis, A. I. = aortic insufficiency, C. E. = cardiac enlargement, H. D. = heart disease.

RESULTS

Group I.—On a maximum of 150 mg. of cortisone daily, twenty-four patients were followed. They represent only a small portion of the admissions for the first three-year period. There were too few cases in the group for the time interval to be significant. As mentioned before, 55 per cent had been sick for over forty-two days on admission and 50 per cent had either

16.6 per cent had no detectable heart disease at the end of the illness, but six patients had smaller hearts and one patient had less murmur after the episode was over, so 29.1 per cent were considered improved.

In summary, almost one-half (47 per cent) were better or had no heart disease, one-third (33 per cent) were the same or worse, and one-fifth (20 per cent) had died.

TABLE V. FORTY-FIVE PATIENTS (GROUP II) GIVEN 200 MG. CORTISONE DAILY

PRETREATMENT DIAGNOSIS	DAY THERAPY STARTED					
	1-7	8-14	15-28	29-42	42-1 YR.	OVER 1 YR.
M. I.	1	1 (1)*	2	1 1*		
M. I. and C. E.	2 (1)	2	3			(2) (1)*
M. I., M. S., and C. E.		1		1 (1)*	2	(2)*
A. I.	1					
A. I., M. V., and C. E.			1	1	2 (1)*	1 1*
M. V. and A. I.		2				
M. I. and M. S.	2 1*	1				
Pericarditis	1					
Myocarditis	1			1		
No H. D.	1		1	1		
POSTTREATMENT DIAGNOSIS						
Murmur and size same	2	3	1	1	1	2
Less murmur, size same	1	1		1		
Same murmur, less C. E.	1	1	2			1
Less murmur and C. E.	1			1	3	1
No H. D.	6	2	4	3	1	
More murmur				1		1
More murmur and C. E.						
Died		1				2

See Table IV for explanation of abbreviations.

TABLE VI. SEVENTEEN PATIENTS (GROUP III) GIVEN 300 MG. CORTISONE DAILY

PRETREATMENT DIAGNOSIS	DAY THERAPY STARTED					
	1-7	8-14	15-28	29-42	42-1 YR.	OVER 1-YR.
M. I.		2	1			
M. I. and C. E.		2				
M. I., M. S., and C. E.			1			(1)
A. I.		1				
A. I., M. V., and C. E.				1 (1)*	1 (1)	
M. I. and M. S.			1			
Pericarditis				1*		
No H. D.	1	2				
POSTTREATMENT DIAGNOSIS						
Murmur and size same			1	1	1	
Less murmur, size same			1			
Same murmur, less C. E.		2			1	1
More murmur			1			
No H. D.	1	5		1		
Died				1		

See Table IV for explanation of abbreviations.

TABLE VII. EIGHT PATIENTS (GROUP IV) GIVEN PREDNISONE

PRETREATMENT DIAGNOSIS	DAY THERAPY STARTED					
	1-7	8-14	15-28	29-42	42-1 YR.	OVER 1 YR.
M. I.		1*				
M. I. and C. E.					(1)	
M. I., M. S., and C. E.					(1)	
A. I.			1			
A. I., M. V., and C. E.			(1)*			(1)
M. S.					(1)*	
No H. D.	1					
POSTTREATMENT DIAGNOSIS						
Murmur and size same		1			1	
Same murmur, less C. E.			1		1	
No H. D.	1		1			
Died					1	1

See Table IV for explanation of abbreviations.

It was the clinical impression of the attending physicians that the drug was a lifesaving measure in three cases. The patients were carefully evaluated and no response to other methods of therapy was being obtained.

Group II.—Of the forty-five patients on the 200 mg. cortisone schedule there were three deaths (6.6 per cent). Two patients had further progression of murmur when drug was started after over twenty-eight days of illness (Table V). Sixteen patients have no heart disease now and only three were without it at the onset. The drug was considered lifesaving in five patients (11.1 per cent).

Group III.—This was comprised of seven patients on the large dosage schedule as seen in Table VI. Of eight patients treated in the first fourteen days of illness, 75 per cent had no residual heart disease. There was only one of the other seven patients who derived so much benefit. There was one death in a patient who had had rheumatic fever for several years with a recent exacerbation.

Group IV.—This smaller group of eight patients included two deaths. Three-fourths of all these patients had either pericarditis or failure at the onset of therapy and the drug was considered lifesaving in three of these (Table VII).

TABLE VIII. DEATHS

CASE	DRUG AND DOSAGE	DURATION OF ILLNESS	DAYS OF DRUG	DIAGNOSIS
E. S.	Prednisone 60 mg.	5 yr.	8 da.	M. I., A. I., and C. E.* Failure
P. B.	Cortisone 150 mg.	3 wk.	36 hr.	M. I. and C. E.* Failure Rheumatic pneumonia
L. M.	Cortisone 150 mg.	4 yr.	8 da.	M. I., M. S. and C. E. Rheumatic pneumonia Failure? Pulmonary embolus?
D. L.	Cortisone 200 mg.	9 da.	4 da.	Pericarditis and C. E.* M. I.—failure Acute rheumatic pancarditis
C. G.	Cortisone 125 mg.	2 mo.	2 da.	Pericarditis* Rheumatic pneumonia Failure Aortic, mitral, tricuspid and pulmonary valvulitis
H. L.	Cortisone 150 mg.	8 mo.	1½ da.	M. I., pericarditis and pancarditis* Rheumatic pneumonia Failure
B. L.	Cortisone 300 mg.	32 da.	14 da.	A. I., M. I., and M. S. C. E.—failure Pericarditis
R. H.	Prednisone 3 courses 40 mg.	10 mo.	3 da. of last course	M. I., M. S., and C. E.* Failure

*Autopsy performed.
See Table IV for explanation of abbreviations.

DEATHS

Table VIII illustrates the deaths. Eight cases, or 8.5 per cent, died while on the drug. It may be readily seen that they were the worst risk patients and on therapy for an average of five days. Four received the drug for three days or less. In seven of the eight cases it was clearly a last-resort measure.

Three other patients have died in this series, but not while receiving the drug. Two of Group II had subacute bacterial endocarditis and died several months later of this infection and heart failure. One other patient in Group I died suddenly of a gastrointestinal illness in another state two years after her hospital discharge. These three cases are not included in the mortality figures above.

COMPLICATIONS

By far the most common problem was the rebound phenomenon. In Group I 12.5 per cent and in Group II 20 per cent had a rebound of consequence. There were none in the Group III patients, but 37.5 per cent of the prednisone-treated patients have been so affected. Others may have suffered a brief slight elevation of C-reactive protein or sedimentation rate but no significant change in their clinical signs or symptoms. Practically all showed the moon facies, some acneform eruption, and weight gain.

The drug was discontinued early in one case where the blood urea rose to over 50 mg. per 100 c.c., and in another when an acute chorea immediately developed a temperature of 40° C. without apparent cause. Edema and ascites were seen six times and congestive failure was increased once. A sustained elevation of blood pressure to around 170/100 occurred in a boy on the 300 mg. schedule, and although the drug was rapidly discontinued, blood pressure has remained elevated to this level six months later. Complete studies for other types of hypertension have been negative.

Transient glycosuria occurred once and mental depression twice. By far the majority of the patients were elated and enjoyed a sense of well-being on the drug. No gastric ulcers were found, although two patients had abdominal pain and upper gastrointestinal series were done. One very ill child had a splenic and liver friction rub during her first week of high dosage therapy. This was thought to be due primarily to the disease rather than to therapy.

DISCUSSION

Ever since Hench and associates[2] suggested this group of drugs for therapy of rheumatic fever, investigations to clarify its position have been in progress. The comprehensive report by the cooperative group was compiled in 1955[3] and did not find any significant advantage of cortisone or ACTH over aspirin in the dosage used. Massell[4] and others have suggested larger doses for more prolonged periods. Markowitz and Kuttner's[5] results have been encouraging with the use of large dosage programs. On the other hand, Harris and his group[6] in Philadelphia are less optimistic, but even they advise steroid therapy for early cases with an intense exudative reaction.

It is our opinion that a 200 mg. dosage schedule for sixty-one days has been helpful but less so than the 300 mg. schedule in altering the course of the disease in early cases. Those on the 300 mg. dosage schedule have more tendency to ascites and edema (four of seventeen cases) and in addition had more complications of increased failure, abdominal pain, hypertension, and depression. The results as regard lessening of cardiac murmurs are better at the end of therapy and there were fewer rebounds in the small group studied.

In eleven cases the drug was considered a last resort and probably a

TABLE IX. RESULTS OF THERAPY AS JUDGED BY DISAPPEARANCE OF MURMURS OR DECREASE IN HEART SIZE ON PATIENTS TREATED IN FIRST TWENTY-EIGHT DAYS OF ILLNESS

GROUP	DOSAGE	PATIENTS TREATED	NO H. D. AT END OF THERAPY	IMPROVED, AS REGARD LESS MURMUR OR SMALLER HEART	TOTAL %, NO H. D. OR BETTER
II	200 mg. cortisone	26	12	7	73
III	300 mg. cortisone	12	6	3	75
IV	60 mg. prednisone	4	2	1	75
Total		42	20	11	73.8

lifesaving measure. In a disease as naturally variable as rheumatic fever this is difficult to judge, but by several experienced observers 12 per cent of Group I, 11 per cent of Group II, and 17.6 per cent of Group III were thought probably to be saved by its addition.

In Groups II, III, and IV, there were thirty-six patients having heart disease at the onset of therapy and treated within the first twenty-eight days of illness. Of these thirty-six, fourteen have no heart disease at the present. This is 36 per cent of the original group. In a symptomatically treated series who were hospitalized and carefully followed before 1948, there were 132 patients with heart disease during a first attack. The duration of their illness was not tabulated. Only twenty-three had no heart disease at the end of three years of observation.[7] This is 17.4 per cent of the original group. We believe that a rough comparison may be made, and conclude that residual heart damage is cut in half by such steroid therapy.

SUMMARY

Ninety-four patients with acute rheumatic fever have been studied and treated at the Medical College of Virginia Hospitals with varying doses of cortisone and prednisone in the past six years. About one-half of the patients on any of the large-dosage schedules treated within 28 days had no heart disease at the end of therapy and 73.8 per cent either had no heart disease or were much improved at the end of therapy (Table IX). There have been eight deaths while on treatment. The drug was considered lifesaving in eleven cases.

Better results were obtained when the drug was started earlier in the course of the disease and in large doses.

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INFLUENCE OF L-LYSINE SUPPLEMENTS ON THE ABSORPTION AND RETENTION OF NITROGEN FROM MILK BY CHILDREN WITH PROTEIN MALNUTRITION

PRELIMINARY REPORT

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ALTHOUGH milk has been shown to be a very good, if not the best, protein foodstuff for the treatment of malnutrition, Albanese[1, 2] has reported on the beneficial effect of feeding milk with added lysine supplements, especially in malnourished children. Therefore, it was decided to try to find out whether absorption and retention of the nitrogen from milk were influenced by lysine supplements in Mexican cases of chronic severe malnutrition. This disease, although variously known in different countries (kwashiorkor in Africa, sindrome pluricarencial in Central America, shibi gachaki in Japan, distrofia da farine in Italy, etc.), has a commonly accepted etiology: a deficient intake of protein foodstuffs of animal origin, due fundamentally to socioeconomic reasons.

MATERIAL AND METHODS

Five male children, all of them having the main characteristic clinical and biochemical signs and symptoms of chronic severe malnutrition,[3, 4] were placed on metabolic beds in order to collect urine and feces separately. The age, body weight, height and the mean theoretical weight for their ages are listed in Table I.

Three of the five children (R. R. F., C. E. N., and M. H. R.) showed clinical pitting edema on admission.

The basal diet consisted of whole cow's milk with added cane sugar. The calorie density was 1 calorie per cubic centimeter. Aliquots of food were analyzed for nitrogen content by semimicro Kjeldahl each time the diet was prepared.

Immediately upon admission the children were fed the basal diet and after two days they were placed on special metabolism beds.

Urine and feces were separately collected during five periods. Each period lasted four days. Small doses of carmine were used to mark the beginning and the end of each collection period.

Each child was fed five times a day. After a control period of four days' duration, L-lysine amino acid was added to the basal diet. Three levels of

Group for Research on Infantile Malnutrition, Hospital Infantil.

Supported in part by a grant-in-aid from Mead Johnson & Company, Evansville, Ind.

this supplement were tested, the doses being 100, 250, and 500 mg. per meal. By giving the supplement with the first sips of milk the intake was assured. A second control period was performed immediately after the last supplemented period. As said before, each collection period lasted four days.

Nitrogen excreted by other routes than urine and feces was not accounted for.

The quantities of milk offered were calculated so as to provide between 100 and 150 calories per kilogram of actual body weight. Table II shows the caloric and protein intake of the children, without taking into consideration the values of the supplement.

TABLE I. CONDITIONS OF THE CHILDREN ON ADMISSION TO THE METABOLIC UNIT

CHILD	AGE (MO.)	WEIGHT (KG.)	HEIGHT (CM.)	MEAN THEORETICAL WEIGHT FOR AGE (KG.)
R. R. F.	29	6.84	82	12.40
C. E. N.	16	5.60	70	9.80
M. H. R.	20	6.52	68	10.60
R. R. J.	36	8.90	84	13.80
C. E. A.	17	6.30	70	10.00

TABLE II. MEAN DAILY INTAKE OF CALORIES AND PROTEINS PER KILOGRAM OF ACTUAL AND "IDEAL" WEIGHTS

CHILD	CALORIES PER KG.		PROTEIN PER KG.	
	ACTUAL WEIGHT	IDEAL WEIGHT	ACTUAL WEIGHT	IDEAL WEIGHT
R. R. F.	154	85	5.277	2.911
C. E. N.	107	61	3.087	1.764
M. H. R.	161	99	6.744	4.148
R. R. J.	118	76	4.940	3.186
C. E. A.	167	105	4.697	2.959

TABLE III. METABOLISM DATA ON THE INFLUENCE OF LYSINE SUPPLEMENTS ON THE NITROGEN BALANCE OF FIVE CHILDREN WITH SEVERE PROTEIN MALNUTRITION (MILLIGRAMS PER KILOGRAM PER DAY, ACTUAL BODY WEIGHT)

CHILD	SUPPLEMENT	NITROGEN INTAKE	NITROGEN EXCRETION			ABSORPTION*	BALANCE
			URINE	FECAL	TOTAL		
R. R. F.	0	844	128	154	282	690	562
	73	703	202	130	332	573	371
	183	724	287	102	389	622	335
	365	1,098	380	209	589	889	509
	0	1,028	444	95	539	933	489
C. E. N.	0	494	165	118	283	376	211
	89	511	194	119	313	392	198
	446	744	306	169	475	575	269
M. H. R.	0	560	152	87	239	473	321
	77	593	188	149	337	444	256
	192	590	234	100	334	490	256
	0	1,079	512	121	633	958	446
R. R. J.	0	649	379	218	597	431	52
	56	660	336	221	557	439	103
	140	665	324	184	508	481	157
	281	692	324	138	462	554	230
	0	790	407	216	623	574	167
C. E. A.	0	715	470	179	649	536	66
	79	730	516	114	630	616	100
	238	769	528	116	644	653	125
	397	799	485	105	590	694	209
	0	752	448	144	592	608	160

*Absorption = intake minus fecal excretion.

RESULTS

Table III presents the metabolism data.

In order to cancel the difference in nitrogen intake due to variable nitrogen content of the milk batches, the following ratio was calculated.

$$\frac{\text{Balance/kg./day}}{\text{Intake/kg./day}} \times 100.$$

With the data thus obtained Tables IV and V were made.

ing a minimum body weight between four and eight days after admission, and then a steady increment.

COMMENT

Nitrogen retentions of similar magnitude to those here presented have previously been reported by Holemans and Lambrechts[5] in Africa, Gómez and associates[6] in Mexico, Hansen and coworkers[7] in South Africa, and Scrimshaw and colleagues[8] in Central Amer-

TABLE IV. NITROGEN ABSORPTION EXPRESSED AS PER CENT OF NITROGEN INTAKE IN SEVERELY MALNOURISHED CHILDREN ON A DIET OF COW'S MILK WITH AND WITHOUT L-LYSINE SUPPLEMENTS

	MG. SUPPLEMENT PER MEAL				
	0	100	250	500	0
CHILD	PER CENT OF INTAKE ABSORBED				
R. R. F.	82	82	86	81	90
C. E. N.	76	77	—	77	—
M. H. R.	84	75	83	—	89
R. R. J.	66	67	72	80	73
C. E. A.	75	84	85	87	81

TABLE V. NITROGEN RETENTION EXPRESSED AS PER CENT OF NITROGEN INTAKE IN SEVERELY MALNOURISHED CHILDREN ON A DIET OF COW'S MILK WITH AND WITHOUT L-LYSINE SUPPLEMENTS

	MG. SUPPLEMENT PER MEAL				
	0	100	250	500	0
CHILD	PER CENT OF INTAKE ABSORBED				
R. R. F.	66	53	46	46	48
C. E. N.	43	39	—	36	—
M. H. R.	57	43	43	—	41
R. R. J.	8	16	24	33	21
C. E. A.	9	14	16	26	21

TABLE VI. WEIGHT CHANGES OF THE FIVE CHILDREN STUDIED

	KILOGRAMS OF BODY WEIGHT		
CHILD	INITIAL	MINIMUM	END OF STUDY
R. R. F.	6.84	5.86 (5)	6.93 (20)
C. E. N.	5.60	4.88 (8)	5.06 (13)
M. H. R.	6.52	6.10 (4)	6.94 (20)
R. R. J.	8.90	8.90 (2)	9.40 (20)
C. E. A.	6.30	6.30 (2)	6.88 (20)

Figures in parentheses represent days after admission.

The weight changes observed in these children during the time of the study (Table VI) were representative of those usually obtained during recovery. The patients who were edematous showed an initial decrease, reach-

ica. All these authors agree that nitrogen retention, although directly correlated to nitrogen intake, is very variable from child to child.

For those not acquainted with chronic protein malnutrition in infants

and children, the figures for retention obtained in these cases might seem almost incredible. Attempts to evaluate the data as functions of body composition are handicapped by reason of the different tissue composition of these patients as compared with normal children of similar age,[9, 10] and because of the fact that rapid changes in fat and water content are characteristic of the initial recovery.[9, 11] Nevertheless, the finding, long known to clinicians working on malnutrition, that the average daily increments of body weight during successful recovery can be ten to twenty times the normal, is of great interest. From Table VI it can be seen that the daily increments of body weight over the minimal, attained at the time when clinical edema disappears, agree quite well with the theoretical values calculated from the balance data.

Attempts to cross-check the magnitude of the retention by way of measuring another component of protoplasm, such as potassium, are not useful, because potassium is retained far in excess of nitrogen, due probably to the chronic potassium depletion present in these children.[9, 12]

The data of this report seem to show that lysine supplements were practically without effect on the absorption and retention of the nitrogen from milk, in the doses used for supplementation in these patients. These findings apparently disagree with the reports of Albanese and co-workers. We have no explanation to offer for this difference in results, unless the severity of malnutrition in our patients is considered. Nevertheless, it seems questionable whether this might be the reason, since children with similar degrees of malnutrition do not show defects in the absorption or retention of nitrogen from proteins of high biological value, such as those found in cow's milk.[5, 6]

Since Albanese's patients did not improve their nutritional status when fed high-protein, high-calorie diets, we are not sure whether or not our patients, who as stated before are representative of protein malnutrition, are similar to those children studied by Albanese and co-workers.

In the possible interpretation of the different results, it is interesting to mention that protein intake was about the same (3 to 7 Gm. per kilogram) both in Albanese's and in our cases.

Data on the urinary excretion of essential amino acids as influenced by the supplements will be reported elsewhere.

SUMMARY

Nitrogen balances were done on five male children affected with chronic severe protein malnutrition while on a diet of cow's milk with and without L-lysine supplements.

Neither the absorption nor the retention of nitrogen from milk was significantly affected by the addition of the supplement.

Up to the present it does not seem justified to use these supplements in the treatment of severe cases of protein malnutrition.

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It is too commonly the case that the entire system of nursery discipline has a direct tendency to call into action, at an early age, the passions of the child—rather than to still them, or to direct them into their appropriate channels. At one time his is dandled and coaxed, in order to quiet him; at another he is scolded and beaten for the very same purpose. We either do what he desires, or oblige him to do what we like: we comply with his whims, or make him submit to ours. Thus no medium is observed; and he is doomed to be always either giving orders or receiving them. The first ideas he forms are those of dominion and slavery; before he can speak he commands—before he acts, he obeys; and sometimes he is corrected before he is conscious of faults, or even before he is capable of committing them. Thus we seize the earliest opportunity of implanting in his tender mind those passions which are afterwards unjustly attributed to *nature*—and having taken pains to render him depraved, we complain when we find him so.

D. Francis Condie: On the Diseases of Children, 1871.

STUDIES ON PROTEIN METABOLISM IN UNDERNOURISHED INFANTS AND CHILDREN

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THE incidence of severe undernutrition in infancy continues, unfortunately, to be high in many countries throughout the world even today. The type of undernutrition encountered in Greece after World War II is usually characterized by freedom from edema and from major manifestations of avitaminosis. In the great majority of cases (96.9 per cent) the undernutrition is simply due to insufficient food intake.[1]

The purpose of this paper is to study the proteolytic activity of the gastrointestinal tract and the rate of absorption of amino acids, as well as the rate of their disappearance from the plasma in undernourished infants and children.

Our approach to this problem has been to determine serially the plasma level of amino nitrogen (amino-N) following (1) the ingestion of casein, (2)) the ingestion of casein hydrolysate, and (3) the intravenous injection of casein hydrolysate. It is evident that the serial determination of the level of the amino-N in plasma following the ingestion of whole protein actually reflects the proteolytic activity in the gastrointestinal tract, provided that the absorption of the resultant amino acids through the intestinal mucosa, as well as their fate after absorption is normal. When predigested protein is given, the amino-N curve expresses the efficacy of the intestinal mucosa in absorbing amino acids, provided that the rate of their disappearance from the plasma after absorption is normal. Finally, the amino-N curve obtained following intravenous administration of amino acids shows, partially at least, the rate of their disappearance from the plasma which is closely related to the rhythm of their utilization.

The indirect evaluation of the proteolytic activity through amino-N curves following protein feeding—in other words, the determination of the results of the enzymic activity following a physiologic challenge—seems to be a better approach to the problem than the direct estimation of the trypsin content in the duodenal juice under static conditions. It is only through the indirect method that the evaluation of the actual potentialities of the proteolytic enzymic system of the gastrointestinal tract is possible. The indirect method has been used by many others,[2-5] but on no occasion, to the best of our knowledge, were the factors of intestinal absorption and rate of disappearance of amino acids from the plasma studied in connection with the proteolytic activity of the gastrointestinal tract.

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The study of each curve independently, as well as the comparative study of the three together, may provide a useful tool in the evaluation of the mentioned processes which are of vital importance for normal growth.

I. PROTEOLYTIC ACTIVITY

When one considers what is known of the physiology of digestion, ingested proteins undergo their first change in the stomach. As a result of the action of both rennin and pepsin, there is a partial breakdown of their molecules into proteoses, peptones, acid metaproteins, and small amounts (less than 3 per cent) of nonprotein compounds. In the duodenum, the above partially digested proteins are acted upon by trypsin and associated proteolytic enzymes produced by the pancreas, which bear the entire burden of hydrolysis to the peptide stage. The hydrolysis is carried to the amino acid stage by aminopeptidases and carboxypeptidases which are secreted by both the pancreas and glands of the intestinal mucosa. The proteolytic pancreatic enzymes are thus indispensable if digestion of proteins is to be adequate. The absorption of the resultant protein-building blocks, the amino acids, obviously causes an elevation of the plasma amino-N level. The above physiologic data make apparent the close correlation between the degree of the elevation of plasma amino-N and proteolytic activity of the gastrointestinal tract, provided always that absorption and rate of disappearance of amino acids from the plasma are normal.

Patient Material.—All the patients included in this study were typical examples of infantile atrophy. Their dietary histories revealed an extremely poor intake for long periods of time, mainly because of repeated episodes of gastroenteritis. However, their diet was essentially a well-balanced one. The appetite had been maintained satisfactorily in most cases but almost all of the patients were apathetic and listless on admission. None of them had generalized or localized edema, changes of skin and hair, or signs of avitaminosis. The serum proteins were determined routinely and found to be in the lower range of normal (5.8 to 6.8 grams per cent). The A/G ratio was above 1 without any exception. Cases not fulfilling the criteria of simple inanition (undernutrition) were carefully excluded from this study.

Twelve infants and children suffering from the above described type of undernutrition, with a mean age of 15½ months (range, 5 to 30 months) and a mean weight of 5,500 grams (range, 3,300 to 8,300 grams) were studied. Obviously the mean body weight was about 50 per cent of the expected.

Fifteen infants and children with a mean age of 13½ months (range, 3 to 24 months) and a mean weight of 9,850 grams (range, 5,200 to 13,500 grams) were used as controls. Infants with fever or diarrhea, or who were given sulfa drugs for the last three days preceding the experiment, were excluded. (Sulfonamides have been shown to invalidate the results of amino-$\frac{1}{3}$N determination by the method used in this study.) The test was always performed within five days after admission.

Method and Procedures.—The plasma amino-N content was determined by the chromatographic method of Frame and associates[6] as this was modified by Fister.[7] The accuracy of the method was assessed by doing 150 determinations on three samples of known concentration in amino-N (4, 8, and 12 mg.). The mean standard deviation was ± 0.15 mg., and the standard error of the mean, ± 0.02 mg.

Within the above limits were found also the sigma values of twelve determinations of amino-N made on each of four specimens of plasma.

All the determinations on plasma samples reported in this study were done in duplicate and in no case did the discrepancy between two determinations exceed three times the standard deviation.

The greater accuracy reported here, compared with the experience of others using the above method of analysis, is probably due to the larger amount of sample used (i.e., 1 ml. of plasma instead of 0.2 ml. of oxalated blood).

The experiment was carried out as follows[2]: the infants were starved for ten hours, after which the first sample of blood was taken. Then a protein meal was given by gavage, consisting of calcium caseinate (Casec). The amount given was 1.72 Gm. (1.5 Gm. of protein = 235 mg. of nitrogen) per kilogram of body weight, diluted in 30 ml. of water. Subsequent samples of blood were taken 30, 75, 135, and 300 minutes after the completion of gavage. During the above period of time no food or liquids were given to the infants and any vomiting or diarrhea, even the slightest, cancelled the test for that day.

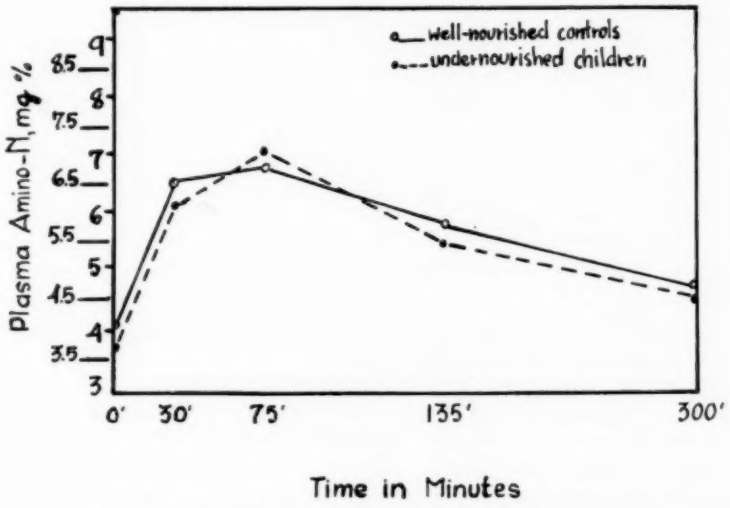

Fig. 1.—Mean amino-nitrogen curves following ingestion of casein.

Results.—Results are shown in Tables I and II. To facilitate the correlation of data, the plasma amino-

N values have been reduced to a zero fasting level. Deviations of these values below the fasting level have been designated as negative quantities.

The maximum elevation of the amino-N, with the only exception of control 1, occurred between 30 and 75 minutes after the protein meal was fed, and the original fasting level

TABLE I. PLASMA AMINO-NITROGEN CHANGES FOLLOWING INGESTION OF CALCIUM CASEINATE (1.72 GM. PER KILOGRAM OF BODY WEIGHT) BY WELL-NOURISHED INFANTS AND CHILDREN
Postprandial values reduced to a zero fasting level

CASE NUMBER	AGE (MO.)	WEIGHT (GRAMS)	PLASMA AMINO-N, MG. %				
			FASTING	30 MIN.	75 MIN.	135 MIN.	300 MIN.
1	24	11,200	3.86	1.90	2.41	2.70	0.36
2	14	9,900	4.74	1.73	2.48	1.10	0.66
3	18	10,300	4.67	2.19	2.63	0.51	0.73
4	18	10,300	4.01	2.05	1.83	1.32	0.95
5	12	9,800	3.94	3.86	4.53	3.72	–0.07*
6	19	11,100	3.65	3.00	2.70	2.12	1.32
7	22	11,500	4.16	3.35	3.21	1.47	0.29
8	10	8,500	4.30	2.70	3.79	2.26	0.66
9	12	13,500	3.86	3.00	2.48	2.56	1.54
10	17	11,100	4.38	3.28	4.67	1.83	1.32
11	5	7,000	3.72	1.47	3.07	1.18	0.36
12	13	10,600	3.65	1.83	1.54	1.32	1.47
13	8	8,100	4.30	2.92	3.14	3.00	1.54
14	3	5,200	3.43	1.61	2.85	1.39	0.29
15	11	9,600	3.72	2.12	2.77	1.40	0.37
	13.7	9,850	4.03	2.47	2.94	1.86	0.79

*Values below the fasting level are designated as negative quantities.

TABLE II. PLASMA AMINO-NITROGEN CHANGES FOLLOWING INGESTION OF CALCIUM CASEINATE (1.72 GM. PER KILOGRAM OF BODY WEIGHT) BY UNDERNOURISHED INFANTS AND CHILDREN
Postprandial values reduced to a zero fasting level

CASE NUMBER	AGE (MO.)	WEIGHT (GRAMS)	PLASMA AMINO-N, MG. %				
			FASTING	30 MIN.	75 MIN.	135 MIN.	300 MIN.
1	30	6,600	4.01	1.54	2.05	1.32	0.59
2	30	8,300	3.79	2.26	4.45	2.16	1.40
3	20	8,000	3.79	3.00	2.56	1.97	1.61
4	8	5,400	3.07	1.10	2.48	1.32	1.10
5	16	5,900	4.38	1.90	2.77	0.51	0.59
6	16	5,000	3.65	2.77	4.89	1.54	1.54
7	16	4,900	3.23	2.92	4.08	1.69	0.22
8	5	3,900	3.94	3.86	5.98	2.85	1.40
9	6	3,300	4.01	2.41	3.28	2.05	0.15
10	20	6,200	3.94	2.41	3.43	3.21	0.00
11	9	4,000	3.65	2.63	2.19	1.47	0.29
12	10	4,600	3.79	1.55	2.48	1.61	0.73
	15.5	5,500	3.77	2.36	3.39	1.81	0.80

The absolute mean values are schematically represented in Fig. 1. As can be seen, in all tested infants, with the exception of control 12, the amino-N level exceeded by 2 mg. per 100 ml. of plasma the fasting level in at least one postprandial sample. was approached within 300 minutes. In most of the cases the value of the last sample exceeded the fasting level; this might be due to continuation of hydrolysis of intact protein for some time beyond the five-hour test period.

Discussion.—It is well known that the main part of the proteolytic activity in the gastrointestinal tract depends on the trypsin enzymatic complex. It is therefore to be expected that the great majority of disturbances of protein digestion are due to inadequate pancreatic function.

A typical example of severe and irreversible pancreatic damage is cystic fibrosis of the pancreas, in which an almost flat amino-N curve with a tendency to rise toward the end of the five-hour period is obtained after oral feeding of whole protein.[2] The peak of the curve never exceeds the fasting amino-N level by more than 1.2 mg. per 100 ml. of plasma.[5]

Considerable decrease of all pancreatic enzymes, as well as severe histologic lesions of the pancreas, has also been described in the syndrome of malnutrition due to an imbalanced diet particularly poor in protein and called by many names such as kwashiorkor,[9, 10] third degree malnutrition,[11] and hypoproteinosis.[12, 13] The mean values for trypsin, amylase, and lipase in a group of cases of kwashiorkor have been reported as being, respectively, one-tenth, one-seventh, and one-fourth of normal.[14] However, the pancreatic lesions are in most cases reversible and the restoration of normal tissue architecture is followed by improvement of both enzymatic activity and clinical picture.

Reduction of pancreatic enzymes has also been described in young infants suddenly deprived of milk even for a short period of time (one to two weeks). Lipase was decreased at first, and later both lipase and trypsin were found to be absent, while amylase could still be detected in small amounts. The resumption of milk resulted in rapid restoration of normal enzymic levels. However, a longer deprivation of milk, the only available source of protein, resulted in severe irreversible histologic damage of the pancreas.[15, 16] It was also found that both enzymatic and histologic changes might occur although the serum proteins and hepatic function tests were normal, and so it was concluded that inhibition of pancreatic activity was one of the early signs of protein deficiency.

The reason for this enzymic suppression is quite obscure. The possibility of the exocrine pancreatic function being influenced by the quality of the previous dietary regimen (i.e., the relationship between substrate and specific enzyme) is a problem that has not yet been elucidated. Grossman and co-workers[17] fed three different groups of mice for three weeks with different dietary regimens and succeeded in obtaining a pancreatic juice rich in amylase but low in trypsin in the group with high-carbohydrate diet and of increased trypsin content in the group fed high-protein diet. The feeding of high-fat diet had little effect on any of the important enzymes. The fluctuations of the three enzymes in the pancreatic juice were preceded by parallel concentration changes in the pancreatic tissue itself.[18] On the other hand, Véghelyi[19] experimented in a similar way, but for a shorter period of time, on six healthy young children and failed to prove any relationship between pancreatic enzymic activity and previous dietary regimen. In any case, the knowledge that the feeding of milk has had a curative effect on the cases of milk deprivation reported by Véghelyi, and that a high-protein

diet has excellent and rapid results in all types of malnutrition due primarily to protein deficiency, leads to the assumption that, despite the pancreatic enzymic suppression, there is a basic proteolytic activity which can provide the organism with the amino acids that are probably necessary for restoration of normal levels of pancreatic function, since these enzymes are usually protein-containing or actual proteins. The likelihood that protein depletion is the cause of the reduction of enzymatic activity in the duodenal content is also supported by the fact that in kwashiorkor many other serum enzymes, such as nonspecific esterase, cholinesterase, alkaline phosphatase, and cholesterolesterase, were found reduced in activity.[20]

From the above-mentioned data it becomes obvious that the suppression of the exocrine pancreatic function is an essential feature of the syndrome of protein depletion.

Concerning the pancreatic enzymic activity, and particularly the proteolytic activity, in infants and children suffering from simple inanition—that is advanced undernutrition on relatively well-balanced diet—there is no unanimity of opinion among the various authors.

It has been traditionally stated that marasmic infants exhibit decreased activity of the various organs, and when depression of the exocrine pancreatic function was detected in three such cases, it was thought that it represented a specific example of this phenomenon.[21] Low trypsin values were also found in three out of ten children suffering from malnutrition of unspecified type.[22]

Recently Bate and James,[5] after performing both direct determinations of duodenal trypsin and plasma amino-N curves following gelatin feeding (the authors use the term "amino acid absorption curves," which is misleading), concluded that the proteolytic activity of the pancreas is depressed in chronic and acute gastroenteritis, as well as in malnutrition in infancy. We think it is fair to mention that the duodenal trypsin was estimated in four out of eight cases of malnutrition included in their study and found to be within normal limits in all four. Amino-N curves were performed in all eight cases and none was normal. It should be emphasized again here that plasma amino-N levels following protein feeding are closely related not only to the proteolytic activity of the pancreas, but also to the processes of intestinal absorption and rate of disappearance of amino acids from the plasma. In view of the fact that these two factors were apparently not considered by Bate and James, and that all tested cases had normal tryptic activity in the duodenal juice, we wonder if their positive conclusion, that the proteolytic activity of the pancreas is depressed in malnutrition, is really justified.

In contrast with the statement made by Bate and James are the results of McDougall,[23] who studied eighteen cases of malnutrition, and after finding with no exception that the pancreatic juice was normal for all three enzymes, concluded that malnutrition in itself does not cause reduced secretion of pancreatic enzymes. In agreement with McDougall's conclusion is the experience of

others[2, 3] who evaluated the proteolytic activity of the pancreas through the determination of plasma amino-N and glycine levels following gelatin and/or casein feeding.

It is evident from the already mentioned data that, although most of the authors agree that simple malnutrition per se does not influence the proteolytic activity of the pancreas, this experience is by no means unanimous.

The slightly confused picture of this problem might be attributed, partially at least, to two factors. In the first place, the results of any study aiming at the evaluation of the pancreatic enzymic activity in undernutrition will certainly be invalidated if patients suffering from protein depletion syndrome (kwashiorkor, etc.) are not excluded. It should be recalled that depression of the pancreatic enzymic activity is an essential feature of the protein depletion syndrome. In the second place, under the present classification of all cases of poor nutrition into two distinctively separated groups, inanition, or undernutrition, or dystrophy, or malnutrition vs. protein depletion syndrome, or kwashiorkor, or third degree malnutrition, or hypoproteinosis, etc., there is no room left for the intermediate types which do not fit in either group. This schematic and therefore biologically inadequate classification is justified only when the typical examples of undernutrition and protein depletion syndrome are considered, because there really are definite clinical, pathologic, and biologic differences between them. The actual existence of intermediate types becomes obvious from the following example: A patient suffering from kwashiorkor may very well weigh, even after complete recovery, no more than 60 per cent of his ideal weight. Such a patient is regarded correctly as suffering from severe undernutrition. The same holds for a severely undernourished infant who may rapidly shift to the protein depletion status if deprived of protein. Of course, the passing from one to the other status of nutrition is not direct but occurs in successive stages which form the clinical, pathologic, and biologic substratum of the intermediate types. However, in the absence of well-defined criteria allowing a more satisfactory classification, we would simply suggest detailed description of the patient material with special reference to the features which differentiate the simple undernutrition from the protein depletion syndrome, since the intermediate types may well present a variety of symptoms and biologic findings which make their inclusion in either major group impossible.

At any rate, the results of this study present additional evidence in support of the view that the proteolytic activity in the gastrointestinal tract is equally effective in both well-nourished and severely undernourished infants and children. This conclusion, based on the similarity of amino-N curves following a whole casein feeding in both well-nourished and severely undernourished infants and children, would not have been drawn without reservations if both intestinal absorption and rate of disappearance of amino acids from the blood stream had not been investigated and found to be normal in undernutrition.

It follows logically from the results of this study that the use of predigested protein or pancreatin instead of whole protein in the feeding of undernourished infants and children does not seem to offer any advantage in the effort of restoration of an ideal body weight.

II. ABSORPTION OF AMINO ACIDS

Amino acids form water-soluble and diffusible molecules and can, therefore, under normal conditions enter both blood capillaries and lymphatic vessels. However, it has been shown that their absorption is mainly effected through the superficial blood capillaries. In some instances the intestinal mucosa may participate actively in the absorption of amino acids,[24] although this does not seem to be the case under normal physiologic conditions.

It has been reported that the rate of absorption of the various amino acids is not the same, and the following was found to be the order of decreasing absorption rate: glycine, alanine, cystine, glutamic acid, valine, methionine, leucine, tryptophane, isoleucine, norleucine, and isovaline.[25] Kratzer,[26] after experiments in the chick, reached the conclusion that the absorption rate varies inversely with the molar volume of amino acid. Shofield and Lewis[27] reported that as the amino group is moved away from the carboxyl group the absorption rate of the substance is decreased. However, more recently, Orten and Johnston,[28] who studied absorption coefficients of sixteen amino acids by chromatographic determinations on an isolated intestinal loop, reached the conclusion that the rate of absorption of the various amino acids is approximately the same.

In the present paper, the rate of absorption of amino acids in severely undernourished and well-nourished infants has been studied by obtaining amino-N curves following the ingestion of casein hydrolysate (Amigen). The absorption of amino acids, and, therefore, the amino-N curve following a test feeding of amino acids, has obviously nothing to do with the proteolytic activity in the gastrointestinal tract. This is only relatively true of Amigen, since it contains a small amount of peptides which are hydrolyzed to the amino acid stage by the proteolytic enzymes. In the case of feeding such a test meal to normal individuals and to patients with defective pancreatic exocrine function, a slight difference is to be expected in the amino-N curve, which would be more elevated in normal individuals. However, since it has already been shown that the proteolytic activity is equally effective in both tested groups, it may be assumed that the proteolysis of the peptides contained in Amigen resulted in equal amounts of amino acids in both undernourished infants and controls. Thus, for the purposes of the present experiment, Amigen may be considered as a pure mixture of amino acids.

The possibility that intact peptides may be absorbed has not been overlooked, but their absorption does not invalidate the amino-N curve since their presence in the plasma would be detected only to a slight extent, if at all, by the method of plasma analysis used.[6]

This study was furthermore undertaken with the purpose of supporting the validity of the amino-N curves

obtained following the feeding of whole protein, since their interpretation may be erroneous if the factors of intestinal absorption and rate of disappearance of amino acids from the blood stream are not taken into consideration.

grams) were tested. All of them fulfilled the criteria of infantile atrophy described in detail in a previous section. Fifteen well-nourished infants with a mean age of 12½ months (range, 5 to 20 months) and a mean weight of 9,750 grams (range, 6,600

TABLE III. PLASMA AMINO-NITROGEN CHANGES FOLLOWING INGESTION OF CASEIN HYDROLYSATE (2 GM. PER KILOGRAM OF BODY WEIGHT) BY WELL-NOURISHED INFANTS AND CHILDREN
Postprandial values reduced to a zero fasting level

CASE NUMBER	AGE (MO.)	WEIGHT (GRAMS)	PLASMA AMINO-N MG. %				
			FASTING	30 MIN.	75 MIN.	135 MIN.	300 MIN.
1	8	9,500	3.79	3.35	4.67	5.18	1.55
2	8	8,100	4.23	6.56	6.41	4.96	0.00
3	16	11,500	3.43	4.81	5.89	7.30	0.81
4	21	12,700	3.35	5.18	6.34	3.28	0.00
5	19	11,000	3.65	5.25	4.96	3.79	0.00
6	13	10,500	3.35	4.23	5.04	3.94	0.10
7	24	12,300	4.53	5.54	5.54	4.60	–0.22*
8	12	10,400	4.16	3.28	5.47	3.72	–0.37*
9	5	6,600	3.50	3.50	4.96	3.79	0.00
10	9	8,600	4.08	4.23	5.25	3.28	0.10
11	8	7,800	3.79	4.38	5.18	2.92	0.00
12	10	9,000	3.94	5.25	4.38	3.50	0.29
13	7	7,500	3.65	4.81	5.40	3.72	0.22
14	9	8,300	4.01	3.35	4.96	4.30	0.29
15	18	12,500	4.38	3.94	6.12	3.35	0.00
	12.5	9,750	3.86	4.51	5.37	4.11	0.18

*Values below the fasting level are designated as negative quantities.

TABLE IV. PLASMA AMINO-NITROGEN CHANGES FOLLOWING INGESTION OF CASEIN HYDROLYSATE (2 GM. PER KILOGRAM OF BODY WEIGHT) BY UNDERNOURISHED INFANTS AND CHILDREN
Postprandial values reduced to a zero fasting level

CASE NUMBER	AGE (MO.)	WEIGHT (GRAMS)	PLASMA AMINO-N MG. %				
			FASTING	30 MIN.	75 MIN.	135 MIN.	300 MIN.
1	29	6,500	3.07	3.65	4.81	4.08	0.00
2	30	8,400	3.94	3.35	5.54	4.74	1.03
3	12	5,800	3.58	6.41	7.52	4.23	0.95
4	9	5,400	3.43	1.83	2.85	1.25	–0.15*
5	5	4,000	3.28	2.77	3.50	3.00	0.00
6	7	3,700	4.45	5.04	6.63	3.50	–0.36*
7	16	5,000	4.16	3.65	5.83	2.12	–0.88*
8	15	5,000	3.65	1.61	3.65	3.28	1.10
9	9	4,000	3.79	3.65	4.81	3.50	0.00
10	10	4,600	3.65	4.16	5.40	3.50	0.29
11	20	6,600	3.94	3.79	4.38	2.92	0.00
12	6	3,500	3.21	2.77	3.35	3.07	0.15
	14	5,200	3.68	3.56	4.86	3.27	0.18

*Values below the fasting level are designated as negative quantities.

Patient Material—Method and Procedure.—Twelve severely undernourished infants and young children with a mean age of 14 months (range, 5 to 30 months) and a mean weight of 5,200 grams (range, 3,500 to 8,400 to 12,700 grams) were used as controls. The plasma amino-N was determined by the above-mentioned method. The experiment was carried out as previously described, the only difference being the use of powdered

casein hydrolysate (Amigen), 2.0 Gm. (= 1.5 Gm. of protein) per kilogram of body weight instead of whole casein (Casec).

Results.—Results are shown in Tables III and IV. Postprandial values have been reduced to a zero fasting level. The mean absolute values are graphically represented in Fig. 2.

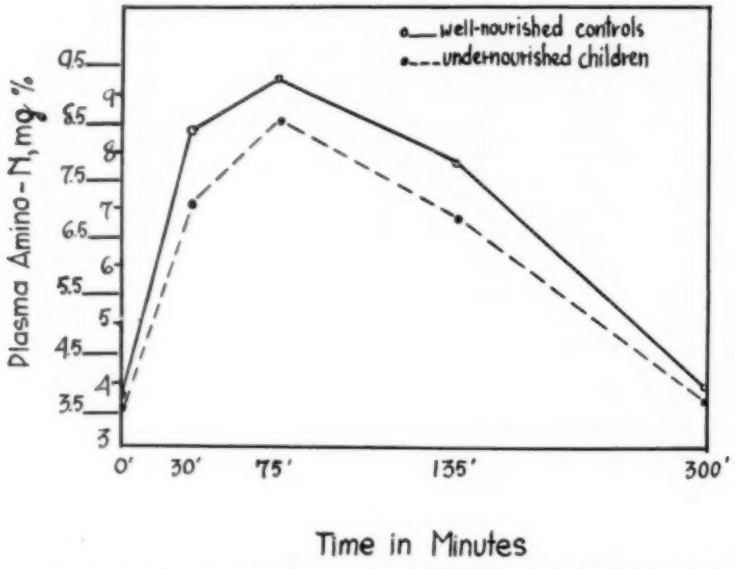

Fig. 2.—Mean amino-nitrogen curves following ingestion of casein hydrolysate.

As can be seen, as early as thirty minutes after the completion of the test feeding, there occurs a sharp rise in the plasma amino-N. In most cases the fasting level is exceeded by 100 per cent. This elevation is consistent and more pronounced in the second postprandial sample. Even after two hours and fifteen minutes the aminoacidemia continues to be high, still exceeding twice the fasting level in most cases. Finally after five hours the original fasting level is again approached. (Values below the fasting level are designated as negative quantities.)

Discussion.—Although the nutritional state of the organism can have a profound effect upon the rate of absorption of materials from the gastrointestinal tract (e.g., thiamine deficiency reduces the absorption rate of glucose, folic acid deficiency reduces the absorption of the fat-soluble vitamins,[29] etc.), there are no known definite clinical entities characterized by abnormally low amino acid absorption. Such a condition can be encountered in the presence of mechanical defects, as, for example, in cases with extremely short gut, or in the case of markedly increased gastrointestinal motility which results in rapid intestinal evacuation, regardless of the

cause. The degree of amino acid absorption has also been studied in normal and hypoproteinemic adults. No difference was found.[30]

In general, the plasma amino-N rises more readily, reaches a higher peak, and is sustained at a high level for a longer period of time after the ingestion of casein hydrolysate than following the feeding of an amount of whole casein having the same nitrogen content (Fig. 3). The same was obbe speculated that when a large amount of amino acids is offered at once, and this is the case after casein hydrolysate feeding, the ability of the various metabolic active organs to use them is exceeded, and so higher and more prolonged plasma amino-N level is obtained. Furthermore it has been shown that, as in the case of glucose, the rate of absorption of amino acids increases when greater amounts are fed.[31] It should be noticed, however,

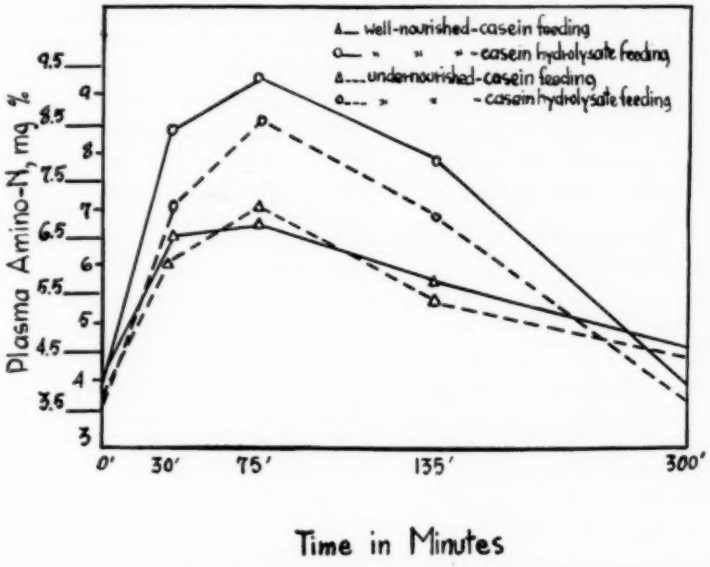

Fig. 3.—Comparison of the mean amino-nitrogen curves following ingestion of whole casein and casein hydrolysate.

served after ingestion of gelatin and has been attributed to its greater aminoacetic acid and alanine content. In the experimental animal these two amino acids give greater and more prolonged aminoacidemia than do any others when fed in equal amounts.[26] However, both calcium caseinate (Casec) and casein hydrolysate (Amigen) contain almost equal amounts of aminoacetic acid and alanine. It may

that after the 135-minute period, a sharp fall of the amino-N level occurs while in the case of whole casein, the last sample (300-minute) almost invariably shows a value higher than the fasting level. This sharp fall may well mean that no more casein hydrolysate is available for absorption sometime between the 135- and 300-minute period. At any rate, whatever may be the interpretation of this difference,

it is common to both tested groups, and, therefore, cannot be attributed to the status of nutrition.

In this study despite individual differences, the mean amino-N curves in both groups resemble each other considerably, the only difference being that the control curve is slightly more elevated than the curve of undernourished infants. However, this difference is not statistically significant, and it may be concluded that the absorption of amino acids is equally satisfactorily performed in both well-nourished and undernourished infants.

The validity of this conclusion is strongly supported by the fact that the rate of disappearance of amino acids from the blood stream was found to be equal in both tested groups.

III. RATE OF DISAPPEARANCE OF AMINO ACIDS FROM THE PLASMA

It is well known that many factors are involved in the synthesis of protein. Genes, electrolytes, enzymes, hormones, and, particularly, insulin[32] and growth hormone,[33, 34] as well as vitamins,[35] play an important role in this complex synthetic mechanism. But the elements from which the protein molecule is built up are the amino acids.

Nine of them are considered as essential for the infant and young child,[36] which means that the young organism cannot synthesize them at all, or at least in sufficient quantities. It is interesting that only eight are essential for the adult.[37] Since the mammalian body neither has nor can create stores in essential amino acids, all of them must be supplied by the diet; the surplus, if any, is either excreted or irreversibly metabolized. Yet this is not enough. Tissue protein synthesis, and hence growth, requires that all the essential amino acids which are to enter into the synthesizing process must be simultaneously available and in adequate proportions during the act of synthesis, since this process is essentially an all-or-none type of mechanism. In other words, "unless a tissue protein can be synthesized at once and completely, it may not be synthesized at all."[38] The repair of lost tissue and protein maintenance are processes essentially similar to protein formation in growth (i.e., the aging protein cannot be mended by a piece-by-piece replacement of the individual amino acids).[39]

Of fundamental importance in protein synthesis is also the caloric adequacy of the diet. Under conditions of inadequate caloric intake the mammalian body tends to consume its available stores of carbohydrate, fat, and protein. Obviously, therefore, if tissue proteins are to be conserved for their specific function, caloric maintenance requirements must be satisfied. However, it should be mentioned that at all levels of caloric intake, protein-depleted animals receiving nitrogen gain more weight or lose less weight than the animals receiving carbohydrates alone, and total body protein parallels the weight changes.[40]

Although it has long been known that the most efficient utilization of protein food requires sufficient carbohydrate and fat, it was only in 1937 that Larson and Chaikoff[41] first showed that there was a time factor in this relationship (i.e., that the achievement of nitrogen balance with a given diet required the synchronous administration of its protein and nonprotein components). Carbohydrate given two hours after consumption of the

diet was about one half as effective in sparing protein, while that given four hours after the diet had no protein-sparing effect.[42]

It should be emphasized that dietary substances fed together with proteins promote growth and utilization of the dietary amino acids, quite apart from their calorigenic sparing action,[43] though the exact mechanism through which the nitrogen-sparing action is accomplished is scarcely known. Suggestions have been made that ". . . carbohydrate spares protein by relieving it of the necessity of providing carbohydrate . . . or that carbohydrate may contribute to the production of amino acids,"[44] and ". . . that the gain in high energy phosphate bonds resulting from metabolism of the extra carbohydrate contributes to the formation of peptides."[42]

Experiments with tagged amino acids in albino rats have shown that the rate of their utilization depends on the previous diet. Thus, feeding the rats for seven days with a diet poor in protein resulted in rapid utilization of the intraperitoneally injected dl-cystine by the plasma and liver proteins. The opposite result was obtained with a protein rich diet.[45]

In the course of our study it was thought that the determination of the rate of disappearance of intravenously injected amino acids from the plasma might shed some light on the rate of their metabolic utilization, which is possibly related to the status of nutrition. Furthermore, the information provided by amino-N curves following intravenous administration of amino acids was necessary for an objective interpretation of the amino-N curves obtained after whole casein and casein hydrolysate feeding. It should be pointed out again that the estimation through amino-N curves of both proteolytic activity in the gastrointestinal tract and intestinal absorption of amino acids might not be valid unless a third factor, the rate of disappearance of amino acids from the blood stream, is considered.

Patient Material—Method and Procedure.—Twelve severely undernourished infants and children aged between 4 and 30 months (mean age, 13½ months) with a mean weight of 5,050 grams (range, 2,900 to 6,600 grams) were tested. As controls, fifteen well-nourished infants and children aged between 4 and 20 months (mean age, 11 months) were used, with a mean weight of 9,050 grams (range, 5,500 to 12,300 grams). All twelve undernourished patients presented the typical features of simple inanition previously described.

The plasma amino-N was determined by the same method. The infants were starved for eight hours, after which the fasting sample was obtained. By the same needle 3 ml. of Amigen per kilogram of body weight was injected at the rate of 1 ml. per minute. The subsequent samples were taken from a different vein 5, 15, 30, and 90 minutes after the completion of the administration of Amigen.

Results.—Results are shown in Tables V and VI. The mean values are represented graphically in Fig. 4.

The amino-N level reaches its highest value at the completion of the injection of casein hydrolysate and then starts declining, so that in the 5-minute sample the increase is 75 per cent above the initial level. The decline continues progressively as the amino-N diffuses into the extracellular space

and then enters the metabolically active cells. It is worth mentioning that in the last sample (90 minutes after the intravenous administration) a value lower than the fasting level was found in eleven of the fifteen well-nourished, and six of the twelve undernourished infants; however, this finding is not statistically significant.

Finally, the mean curves resemble each other, and no difference between the rate of amino acid disappearance from the plasma of well-nourished and undernourished infants was detected.

Discussion.—As it has already been mentioned, an adverse relationship has been shown between protein content of diet fed to albino rats and rapidity of dl-cystine utilization.[45] Quite different is the experience of Levey and associates,[46] who administered a solution of amino acids intravenously to

TABLE V. PLASMA AMINO-NITROGEN CHANGES FOLLOWING INTRAVENOUS ADMINISTRATION OF CASEIN HYDROLYSATE (3 C.C. OF AMIGEN 5 PER CENT PER KILOGRAM OF BODY WEIGHT) IN WELL-NOURISHED INFANTS AND CHILDREN
All values reduced to a zero fasting level

CASE NUMBER	AGE (MO.)	WEIGHT (GRAMS)	PLASMA AMINO-N, MG. %				
			FASTING	5 MIN.	15 MIN.	30 MIN.	90 MIN.
1	8	7,500	4.67	2.63	0.80	−0.29*	−1.47*
2	11	9,000	3.72	3.58	1.98	0.80	−0.51*
3	4	5,500	3.35	2.77	1.76	1.03	0.22
4	9	8,300	4.01	1.90	0.95	0.29	−0.66*
5	12	10,000	4.38	2.05	0.88	0.73	−0.81*
6	5	6,600	3.35	2.56	1.76	0.37	−0.37*
7	9	8,600	4.08	2.92	1.40	0.66	0.10
8	8	7,800	3.72	3.28	1.98	0.95	0.00
9	18	11,100	3.35	2.70	1.32	0.10	−0.21*
10	13	11,700	4.23	3.43	0.73	0.22	−0.15*
11	10	9,000	4.01	2.92	1.32	0.36	−0.36*
12	12	10,000	3.72	2.77	1.76	0.66	0.00
13	14	10,000	4.08	2.92	1.83	0.81	−0.51*
14	8	8,000	4.23	3.43	1.40	0.66	0.00
15	24	12,300	4.38	2.70	1.32	0.10	−0.21*
	11	9,050	3.95	2.84	1.41	0.50	−0.33*

*Values below the fasting level are designated as negative quantities.

TABLE VI. PLASMA AMINO-NITROGEN CHANGES FOLLOWING INTRAVENOUS ADMINISTRATION OF CASEIN HYDROLYSATE (3 C.C. OF AMIGEN 5 PER CENT PER KILOGRAM OF BODY WEIGHT) IN UNDERNOURISHED INFANTS AND CHILDREN
All values reduced to a zero fasting level

CASE NUMBER	AGE (MO.)	WEIGHT (GRAMS)	PLASMA AMINO-N, MG. %				
			FASTING	5 MIN.	15 MIN.	30 MIN.	90 MIN.
1	7	3,500	3.21	2.34	1.32	1.25	0.29
2	30	6,600	3.07	2.41	1.25	0.59	−0.15*
3	30	8,300	3.43	2.85	2.05	1.54	0.51
4	12	5,900	4.01	2.92	1.83	0.80	−0.65*
5	9	4,600	4.53	3.79	2.12	1.47	1.18
6	6	2,900	4.01	3.65	2.12	0.80	−1.10*
7	8	5,200	3.28	3.21	1.98	1.51	−0.07*
8	20	6,200	3.94	4.16	2.56	1.18	0.22
9	4	3,800	3.43	2.77	1.76	0.88	0.29
10	16	4,900	3.72	2.41	0.66	--	−0.95*
11	16	5,000	3.14	2.70	1.55	1.10	0.07
12	6	3,500	3.21	2.05	1.10	0.15	−0.66*
	13.7	5,050	3.58	2.94	1.69	0.94	−0.09

*Values below the fasting level are designated as negative quantities.

four healthy adults and an equal number of malnourished adults, and subsequently estimated the amino acid content of the urines by microbiologic methods. Their results, as well as the experience of others,[47] suggested that there is no relation between previous dietary regimen or state of nutrition of the human organism and amino acid retention. The undernourished infants and children included in the present study did not show any clinical evidence of hypoproteinemia, and the serum proteins have been found on several occasions to be within the lower limits of normal. However, the fact that their mean age was 13½ months old, while their mean weight was only 5,050 grams, leads to the assumption that their diet, although well-balanced, had been inadequate for a long period of time, and that the nutritional deficiency also concerned protein. Furthermore, that the inadequate caloric intake had resulted in considerable consumption of the stores of carbohydrates, fat, and protein. At any rate, we think that the nutritional status of our patient material is similar to that of the malnourished adults reported by Levey and co-workers[46] and different from the status of acute protein depletion of the albino rats who exhibited rapid incorporation of S^{35} labeled cystine into their body protein.

The intravenous administration of 3 ml. of Amigen per kilogram of body weight provides, simultaneously, 150 mg. of glucose and 12 mg. of amino-N, most of which is contained in essential amino acids; in other words, the above-mentioned prerequisites for a satisfactory protein-synthesizing process are entirely fulfilled.

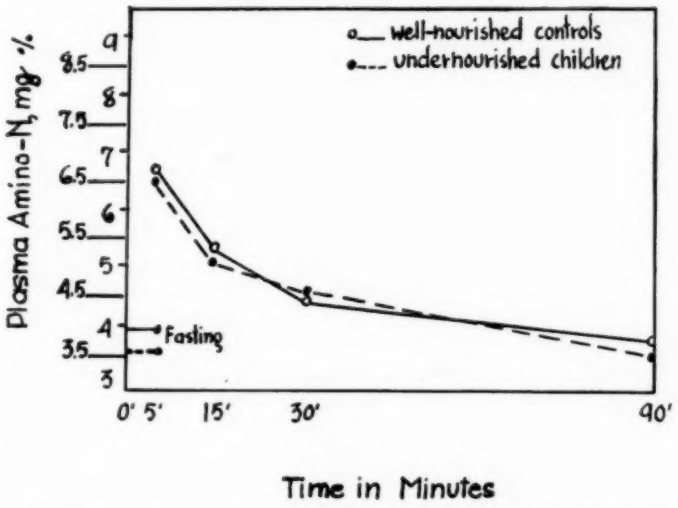

Fig. 4.—Mean amino-nitrogen curves following intravenous injection of casein hydrolysate.

It is well known that after the intravenous administration of protein hydrolysate a certain amount of amino acid escapes through the kidneys. This amount varies with the experimental animal used, rate of administration, etc., and is reported to be as low as

2.4 per cent[48] and as high as 10 to 15 per cent.[49] In view of the relatively small amount of amino acid excreted by the kidneys, as well as the data concerning the excretion of amino acids in malnourished adults,[46] it was assumed that although a slight difference in the renal loss of amino acids between the two groups of tested infants could not be excluded, it would not be great enough to materially affect the plasma amino-N curves.

Comparable experiments in mice have shown that 90 per cent of the amino acids disappear from the plasma 25 minutes after the intravenous injection of casein hydrolysate and accumulate during the above period of time primarily in the liver and kidneys, which are organs with high metabolic activity,[50] and to a lesser extent in the skeletal muscles.[51]

It was also shown that neither the liver, the main deaminating organ, nor the pancreas influences the rate of amino acid disappearance from the plasma after intravenous loading,[52] which probably means that for a certain period of time amino acids are utilized exclusively in anabolic processes.

From the above, it can be assumed that the serial determination of the amino-N of the plasma in a relatively short period of time after intravenous loading with casein hydrolysate may measure the rate of their anabolic utilization.

In any case, our results show that severe undernutrition in infants and young children does not interfere with the rate of amino acid assimilation, as the evaluation of this process was attempted by us, and that the load test used for the evaluation of the nutritional state in regard to certain vitamins does not appear applicable to the study of protein nutrition.

CONCLUSIONS AND SUMMARY

1. An attempt was made to study some aspects of protein metabolism in infants and young children suffering from severe undernutrition. Criteria were defined for the differentiation of patients suffering from severe undernutrition due to an inadequate but otherwise well-balanced diet from those with the protein depletion syndrome better known as kwashiorkor, third degree malnutrition, hypoproteinosis, etc.

2. Plasma amino-N curves were obtained following (a) the ingestion of whole casein for the study of the proteolytic activity in the gastrointestinal tract, (b) the ingestion of casein hydrolysate for the study of the intestinal absorption of amino acids, and (c) the intravenous administration of casein hydrolysate for the study of the rate of disappearance of amino acids from the blood stream. The plasma amino-N level following whole casein feeding depends not only on the proteolytic activity in the gastrointestinal tract, but also on the rate of amino acid absorption, as well as on their metabolic fate. It is evident that the plasma amino-N level after casein hydrolysate feeding depends on both intestinal absorption and rate of disappearance of amino acids from the blood streams. Hence, curves b and c are necessary for an objective interpretation of curve a, and curve c should always be considered in the interpretation of curve b.

3. The proteolytic activity in the gastrointestinal tract was found to be

equally effective in fifteen well-nourished and twelve severely undernourished infants and young children that were tested. In view of this finding, it was suggested that formulas consisting of predigested protein are not necessary in the feeding of undernourished infants.

4. The rate of absorption of amino acids through the intestinal mucosa was found to be equal in fifteen controls and twelve severely undernourished patients. Although the range of individual variations was quite wide in both groups, the conclusion that amino acid absorption remains intact in severe undernutrition may safely be drawn.

5. Experimental work proved that protein-depleted animals show faster incorporation of labeled amino acids into tissue protein. Under the conditions of our experiment no difference was detected in the rate of amino acid assimilation by twelve severely undernourished patients compared with fifteen well-nourished infants and children. Such a result was to be expected, since undernourished infants, although exhibiting a chronic reduction of their protein store, do not suffer from acute protein depletion.

6. The multiplicity of the etiologies and pathogeneses of the various types of poor nutrition in infancy and childhood dictates the need for a more precise terminology than the existing one. Until better-defined criteria are established for the differentiation of the various types of poor nutrition, it is suggested that all clinical, pathologic, and biologic findings derived from such cases be accompanied by detailed description of the patient material instead of being vaguely attributed to "malnutrition."

I am grateful to Professor C. Choremis for his constant encouragement and helpful criticism during the preparation of this paper.

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Military Honors

Ebebezer Griffen, born December 26, 1770, "and departed this Life in Cambridge & was Buried by the Honners of war. this was dun in Consequence of the Childs Death being Caused by his eating Nuts which was gave him by the Commanding Officer of the Regiment of Continental Soldiers that was Stationed there at that time and his father being an Officer in the Regiment it was dun to Honner him."

ESSEX INSTITUTE HISTORICAL COLLECTIONS.

THE MANAGEMENT OF FACIAL TRAUMA IN INFANTS AND CHILDREN

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IN RECENT months we have encountered a large number of infants and children with improperly managed facial wounds. Despite the numerous excellent reports on the management of trauma, facial injuries in infants and children continue often to be treated inadequately, and this circumstance prompts this communication. The physician rendering the initial care has the optimum chance to bring about a satisfactory final result. The initial care of facial injuries and lacerations requires much more time and effort than is generally felt necessary, if a satisfactory final result is to be obtained. Scar tissue developing, both deep and superficial, in the soft tissues and skin makes secondary plastic revision difficult, and the eventual result often is far from gratifying. The conspicuous and disfiguring facial scars which result from inadequate initial surgery may represent a real catastrophe, often with long-lasting mental fixation for the patient.

During the early stages of ambulation the child is subject to frequent falls and tumbles. Common sites of trauma are the supraorbital and submental areas and the lips.

By virtue of his stature a child's face presents a readily accessible target for the tormented dog or cat. Animal bites result in ragged, lacerating wounds about the mouth, cheeks, and nose. Falls on macadam streets and play areas surfaced with concrete result in contused abrasions about the cheeks, nose, and forehead, often with deep surface abrasion in which cinders and dirt are embedded. Such particles of dirt and foreign matter result in a permanent, disfiguring tattoo if treated inadequately.

A few remarks concerning the psychologic aspects of facial trauma are pertinent. Once the injury has occurred, the frightened and often actively bleeding child is rushed to the nearest medical facility. Recognizing the possibility that disfiguring facial scars may result, the parents may be inordinately worried. In these new surroundings and with a painful wound, the child regards as an enemy any strange person approaching. It is of paramount importance that the attending physician evidence kindness, sympathy, and great patience. A child will readily discern the truly sympathetic approach as opposed to a superficial exhibition by the physician. Each move in the examination and treatment must be slow, deliberate, and gentle. If the child is sufficiently

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This work was aided by a grant from the John A. Hartford Foundation, Inc., and from United States Public Health Service Grant D-319.

adult that one may reason with him, the wise physician will sit down and take all the time necessary to offer in simple and honest terms an explanation of exactly what is to be done. The majority of children will accept small amounts of pain if they are expecting it and understand that it will last for only a brief interval. Time spent thus will be rewarded amply by confidence and full cooperation on the part of the small patient.

As for the injury, hemorrhage must be arrested and an adequate airway must be ensured. Simple pressure with a sterile gauze pad will usually arrest hemorrhage. An older child should be made to feel that he is helping the physician by being allowed to hold the pad over the wound. A brief history is obtained next, and a general physical examination carried out. Specifically a history of unconsciousness should be sought, as well as epilepsy, blood dyscrasia, and drug sensitivity. As in all cases of trauma, one must be certain that multiple injuries do not exist.

The first inspection of the wound should be undertaken in a quiet room, and with good light. Frequently this examination will be more successful if the parents can be persuaded to wait in another room. Initial appraisal of the wound serves two purposes: a plan of management for the wound should be made, such as the room in which the repair is to be carried out (emergency or operating room) and the type of anesthesia best suited to the case, and, second, an assay of the damage to soft tissue and underlying bone is made. Often a sterile gauze pad saturated with 2 per cent procaine hydrochloride solution applied to the wound for a few moments will confer adequate anesthesia to permit relatively painless palpation of the base of the wound with a sterile gloved finger. This is not the time for probing, elevating skin flaps, or evacuating hematomas. If on palpation of the underlying bone there is any question of skull or facial bone fracture, x-rays should be obtained promptly. Rarely will an infant or young child cooperate for the administration of local infiltration anesthesia, and a strong plea is made for more frequent use of general anesthesia. Every physician has witnessed the traumatic and undignified spectacle of a screaming, cyanotic, and acrobatic child being forcibly restrained by distraught parents and frightened attendants while a short-tempered intern struggles to place sutures accurately in the moving target that is the facial laceration. Such demonstrations are reminiscent of surgery in the days prior to the advent of anesthesia. How infinitely more satisfactory is the careful and meticulous care and suturing of the wound that a few moments of general anesthesia will afford! Admittedly the use of general anesthesia requires admission to the hospital, parental consent, blood count and urinalysis, the convening of anesthetist and operating room team, and increased expense. Notwithstanding these arguments, deep and extensive facial lacerations, and especially those about the eyes and mouth, can receive optimum initial care only in the operating room with the patient under general anesthesia. The end results of such detailed initial care fully justify the time, effort, and expense involved.

When the initial examination of the wound and the patient indicates that

local anesthesia may be used, we have found oral or parenteral short-acting sedatives to be a helpful adjunct. The local anesthetic agent of choice is 2 per cent procaine hydrochloride. This drug concentration permits the use of a small quantity of injected solution, with less distortion of the tissues, and gives excellent anesthesia. The addition of epinephrine hydrochloride is seldom necessary.

In the case of the small, incised, clean laceration upon a flat surface of the face or chin, without bleeding and without underlying bone destruction, it is often possible to obtain accurate approximation of the skin edges by applying flamed adhesive strips. These "butterfly" strips are prepared commercially, however, and are sterile, so they do not require flaming. Compound tincture of benzoin applied to the skin surrounding the laceration will increase the adhesive qualities of the tape. This effective and often neglected method of managing the small clean laceration obviates the problems of anesthesia, suturing, and removal of sutures. Wounds about the eyes and mouth should not be managed by this form of therapy. Metal skin clips advocated for closing scalp lacerations have no place in the management of lacerations of the face, and their use is strongly decried. The fundamental concepts of wound healing which must be adhered to in every case of facial laceration are as follows:

1. Thorough cleansing of the wound.
2. Retention of no foreign matter in the wound. This includes tissue strangulated by improperly placed ligatures, large knots of suture material, and long suture ends.
3. Absolute hemostasis.
4. Exact approximation of muscle, obliteration of dead space by suturing fat with knots buried, and coaptation of skin edges, without tension.
5. The use of the finest suture material appropriate, usually 5-0, 6-0, and 7-0.

When suturing of the wound is indicated, the wound should be washed with plenty of warm water and soap of a bland nature. The skin surrounding the laceration is prepared with antiseptic solution and appropriate sterile drapes are applied.

If the treatment is being carried out under local anesthesia it is well to arrange drapes in such a way that the child can see what is being done. While it may be necessary to clip sideburns or hair on the scalp, the eyebrows should never be shaved, as occasionally they will not grow in again. The laceration is irrigated with approximately 1 liter of warm sterile saline solution and, if the tissue is contused and lacerated with ragged and uneven edges, a limited débridement is carried out. This consists of excision of devitalized tissue only, and never the entire wound margin. Because of the abundant blood supply of the face, good wound healing occurs even in cyanotic skin flaps, so an absolute minimum of tissue should be sacrificed. Actual loss of facial skin rarely occurs.

Sutures in the skin itself should be placed 2 to 4 mm. apart and the point of entrance and exit of the needle should be 2 to 3 mm. lateral to the wound margins. If the sutures are placed farther back from the lips of the wound, ugly, indented, crosshatching scars will result. If the needle is

inserted too close to the wound margins, difficulty will be experienced when removing the sutures. Sutures should not be permitted to remain in the facial skin longer than forty-eight to seventy-two hours. All knots should be tied on the same side of the wound and each knot situated at the site of the needle puncture in the skin. This precaution will allow easy suture removal. To remove sutures, the rounded blade of a small scissors may be slipped easily under the suture on the side opposite the knot, and each suture is cut. Removal is then accomplished relatively painlessly, if thirty seconds to a minute are allowed to transpire before sutures are removed. This short pause will allow the natural skin resiliency to loosen the sutures, making their removal easy and painless. One often sees sutures removed by pulling the knot up away from the skin and cutting the suture, which is under tension. This method is painful and should be abandoned.

Animal bites are contaminated and therefore potentially infected wounds. The barbaric practice of cauterization of these wounds with fuming nitric acid or other necrotizing agents is mentioned, to be condemned strongly. The Health Department of the City of New York no longer requires this form of treatment. Such wounds should be cleansed thoroughly with soap and water and sterile saline solution. Ragged edges and devitalized tissue should be débrided, excising an absolute minimum of tissue, and a primary closure effected. To leave these wounds open and permit healing by secondary intention only leaves disfiguring scars. Animal bites are often located about the nose or mouth and especial care must be taken to approximate the vermilion border accurately. Tetanus immunization and antibiotics must be used in these injuries. Rabies vaccine should be considered under the following circumstances:

1. If the animal is rabid or becomes sick within seven days of the biting.
2. If the animal escapes, is unknown, or otherwise unavailable for observation.

It must be remembered that—in addition to dogs—bats, badgers, squirrels, foxes, wildcats, or wolves may be rabid. If rabies vaccine is indicated, it does not matter that the animal has been vaccinated. When indicated, hyperimmune antirabies serum* in doses of 0.5 c.c. per kilogram of body weight may be administered within twenty-four hours after the bite, but only after testing the patient for sensitivity to horse serum. The antiserum bridges the gap between the onset of vaccine treatment and the formation of antibodies.

Large mucosal lacerations should be carefully approximated with fine catgut. Small mucosal puncture wounds, such as result from a lollipop stick, usually heal without treatment. As a result of trauma infants may herniate the buccal fat pad (sucking pad) into the oral cavity, and this bulging mass of adipose tissue should be carefully replaced and the overlying mucosa sutured. Teeth may be fractured or loosened by falls and prompt appraisal by a dental consultant should be sought, especially if there be bleeding from the tooth socket, actual fracture, or discoloration of the teeth.

In the case of a deep surface abrasive injury, general anesthesia is pre-

*Product of Lederle Laboratories, Division of American Cyanamid Company.

ferred to local. The traumatized area should be washed with bland soap and water and all surface dirt removed. Embedded particulate matter may require the use of a sharp scalpel blade, an ophthalmic spud, or sand or emery paper for removal. Emery paper may be autoclaved and wrapped around a sterile gauze roll and used thus as a sanding block. A small piece of abrasive paper may be rolled about the jaws of a Kelly clamp for use about the ala nasi and other relatively inaccessible areas. It is often a tedious and time-consuming job to remove each bit of foreign matter from the skin, but, if it is not done, an indelible tattoo will result. Surface abrasive injuries may be dressed with a layer of petroleum jelly gauze applied to the skin, with an overlying sterile fluff compression dressing.

Proper dressing for facial injuries must be used, as children will pick at and dislodge dressings loosely applied. An external dressing of flannel gauze made adherent by a commercially prepared liquid surgical adhesive will provide a dressing which will remain in situ for from three to four days. With infants, it is wise to encircle the head with a roller gauze bandage, to ensure that the dressing will stay in place. With older children, after the wound is sealed, in twenty-four hours, it is feasible often to leave the wound open to the air without a dressing. If one applies a thin film of petroleum jelly or a piece of ointment gauze to the wound at the time of the first dressing, subsequent changes of dressings will be facilitated without pulling away the new surface epithelial cells.

In summary, this communication constitutes a plea for more careful, scrupulous, and considerate care of facial trauma in infants and children. The basic principles necessary for good wound healing have been reviewed. General anesthesia will simplify and expedite the operative procedure and afford the most favorable circumstances for a good end result. As in all aspects of pediatric surgery, children are entitled to the best that surgical care has to offer. Certainly, the young patients who receive inept and lightly regarded care of facial injuries will become objects of interest and perhaps torment by their contemporaries. At best, a poor result can be corrected but only as a consequence of a secondary operation which will do only what might or should have been done initially.

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NIEMANN-PICK DISEASE IN A BOY OF 16 MONTHS

Electrophoretic Study of Blood Serum Proteins and Lipoproteins Following Various Types of Therapy

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NIEMANN-PICK disease, a variation of Gaucher's disease, is a condition involving a disturbance of metabolism affecting the spleen, liver, nodes, and marrow and exhibiting the typical lipoid-filled foam cells seen in the adrenal, pancreas, thymus, and other tissues. The case described here presents the usual picture outlined above, as well as lipid histiomytosis of the phosphate type with chronic hepatosplenomegaly, and falls into the age limit usually characteristic of the disease, which is one primarily of infancy. However, Pfandler[1] described a few examples in older children and two adults, and Burne[2] tells of a case in a fetus of full term. The disease is rare and usually fatal in infancy, and according to Thannhauser[3] only about seventy cases had been reported up to 1947.

The disease in the case described, associated with complications of bronchial involvement and finally hypostatic pneumonia, proved fatal. Data are here presented regarding the use of various types of therapy employed, such as cortisone, vitamin A, vitamin B_{12} along with lipoproteins (choline and methionine), ACTH, and antibiotics (Mysteclin, streptomycin, Chloromycetin, Terramycin), in an attempt to halt or delay the progress of the disease. Though, in the final analysis, these did not prove fruitful under the conditions and duration of treatment prevailing in this case, it is hoped that the information presented may shed some light on the disease and perhaps encourage renewed efforts in an attempt to clarify its etiology and treatment.

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MATERIALS AND METHODS

A white, poorly developed male of 16 months weighing 17.4 pounds was admitted, with a final diagnosis of Niemann-Pick disease and associated hepatosplenomegaly based on chemical, histological, physical, and marrow findings. Therapy was aimed in many directions with the use of special diets, steroid therapy, antibiotics, and large doses of vitamins. Following each of these regimes of treatment, blood was obtained by venipuncture and analyzed for hemoglobin, red blood cells, white blood cells, reticulocytes, lymphocytes, neutrophils, and platelets. Sodium and potassium ions were analyzed by flame photometry. Chlorides were determined by the method of Schales and Schales.[4] Urea was determined by the Karr method.[5] Total serum cholesterol and cholesterol esters were done according to the method of Bloor and

Knudson.[6] Serum proteins and lipoproteins were determined by the use of paper electrophoresis in the following manner. Eight Whatman 3 MM paper strips, 2.9 by 30.0 cm., were run simultaneously in a hanging strip type cell.[7] The strips were allowed to equilibrate in the cell with a Veronal buffer at pH 8.6 and 0.05 ionic strength. Serum (0.01 ml., or 10 lambda, for protein determinations and 0.05 ml., or 50 lambda, for lipoprotein determinations) was then applied from a micropipette and special applicator to the apex of the strips, directly over glass supporting rods. Separation was carried out with a constant current of 5 ma. for eight strips (90 to 100 volts) for sixteen hours at room temperature. The strips were then removed from contact with the feed wick, spread flat on a rack, and dried in an oven at 90° to 120° C. for thirty minutes. The strips were transferred to a staining rack and stained with bromphenol blue for the protein pattern and with Oil-Red-O for the lipoproteins. The protein patterns were then rinsed three times—for five, five, and ten minutes—in 2 per cent acetic acid (v/v) and then for five minutes in a 2 per cent sodium acetate solution made up in 2 per cent acetic acid. After blotting gently on clean filter paper, the strips were transferred to a drying rack and dried in the oven for eight to ten minutes at 90° to 120° C. The lipoprotein patterns were stained for sixteen hours at 30° C., washed thoroughly in tap water, blotted as above, and dried for eight to ten minutes at 90° to 120° C. All dyed strips were then scanned with an automatic recording and integrating scanner of the SpinCO-Servo type whereby the area under the density curves is shown by a corresponding series of pips. For accurate readings, the light source of the scanner was varied by an adjustable slot (narrow slit for the protein patterns and wide slit for the lipoprotein patterns). No special filter was employed for either of the pattern complexes.

Patterns were taken initially and after each regime of therapy. Normal values were obtained from the literature.[8]

RESULTS

The serum proteins occur as five bands, depicted in Figs. 1 to 7, with corresponding paper strips in the order of increasing mobility: gamma, beta, $alpha_2$, $alpha_1$, and albumin fractions. Fig. 8 demonstrates a breakdown of the respective albumin and globulin fractions following the various forms of therapy. The lipoprotein curves, Figs. 9 and 10, were analyzed into three components: a pale alpha fraction corresponding predominantly to the $alpha_1$ globulin and some $alpha_2$, an intensely stained beta fraction corresponding to the beta and gamma globulins of the protein curve, and a gamma fraction related to the gamma globulin, but said not to contain lipids.

Table I illustrates the values for the various protein fractions and Fig. 1 is illustrative of a normal pattern. It is noted in Figs. 1 to 8 that, initially, the albumin/globulin (A/G) ratio is significantly increased when compared to the normal values, as a result of a significant increase of the albumin fraction with the other fractions being correspondingly low and at the lower limit of the normal scale. Cortisone, ACTH, and antibiotics (Mysteclin, streptomycin, Chloromycetin, Terramycin) significantly decreased the A/G ratio to a point even

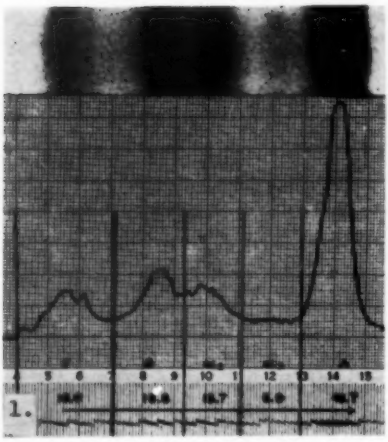

Fig. 1.

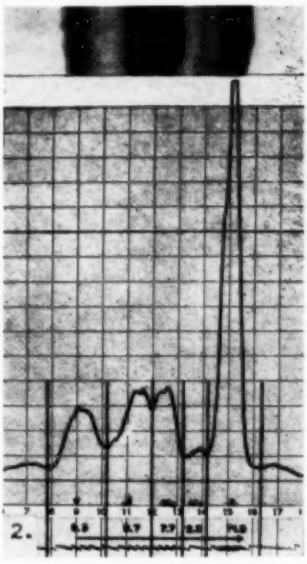

Fig. 2.

Figs. 1 to 7.—Electrophoretic patterns and curves for albumin and globulins. *1*, Normal curve. *2*, Initial curve. *3*, Seven days post cortisone. *4*, Post vitamin B_{12} and lipoproteins. *5*, Post ACTH. *6*, Seven days post vitamin A. *7*, Post antibiotics.

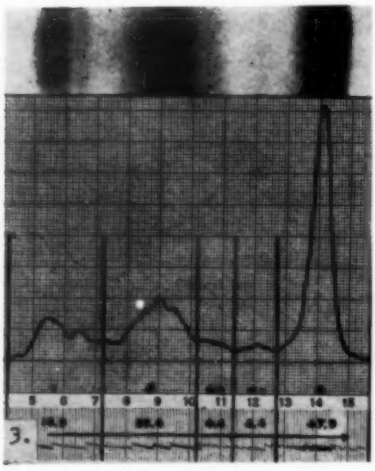

Fig. 3.

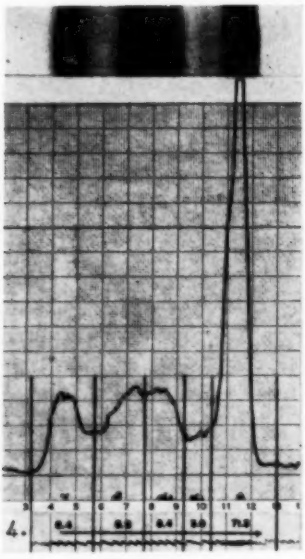

Fig. 4.

TABLE I. PAPER ELECTROPHORESIS. SERUM PROTEINS

TREATMENT	ALBUMIN (%)	ALPHA$_1$ (%)	ALPHA$_2$ (%)	BETA (%)	GAMMA (%)	A/G (%)
Normal	49.6-69.0	1.06-16.7	7.56-16.3	6.3-20.8	6.89-18.6	.98-2 3
Initial	73.2	3.3	7.4	8.8	7.3	2.70
7 days post cortisone	46.7	6.0	13.7	18.6	15.0	.87
Post B_{12} and lipoproteins	71.0	2.3	7.7	9.7	9.3	2.40
Post ACTH	47.9	4.4	4.4	26.4	16.9	.80
7 days post vitamin A	71.3	3.0	8.4	8.9	8.4	2.50
Post antibiotics	41.8	6.3	10.1	21.5	20.3	.72

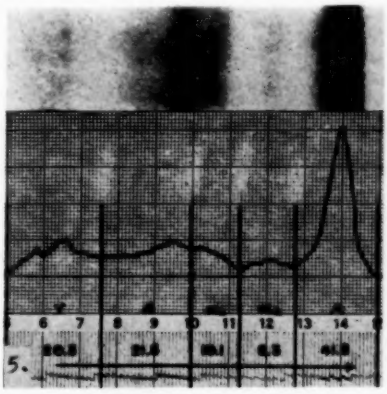

Fig. 5.

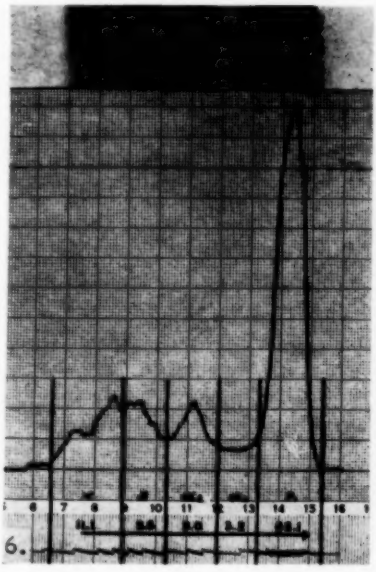

Fig. 6.

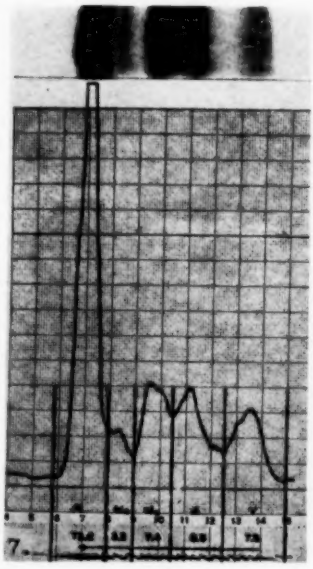

Fig. 7.

below normal, as a result of marked decreases in the albumin levels, with slight increases of the alpha$_1$, increase of alpha$_2$ with cortisone and antibiotics, but with ACTH a decrease of apparent significant effect on the A/G ratio, which maintains its high level above normal and indicates no change in any of the fractions except for a slight rise in the gamma globulin with

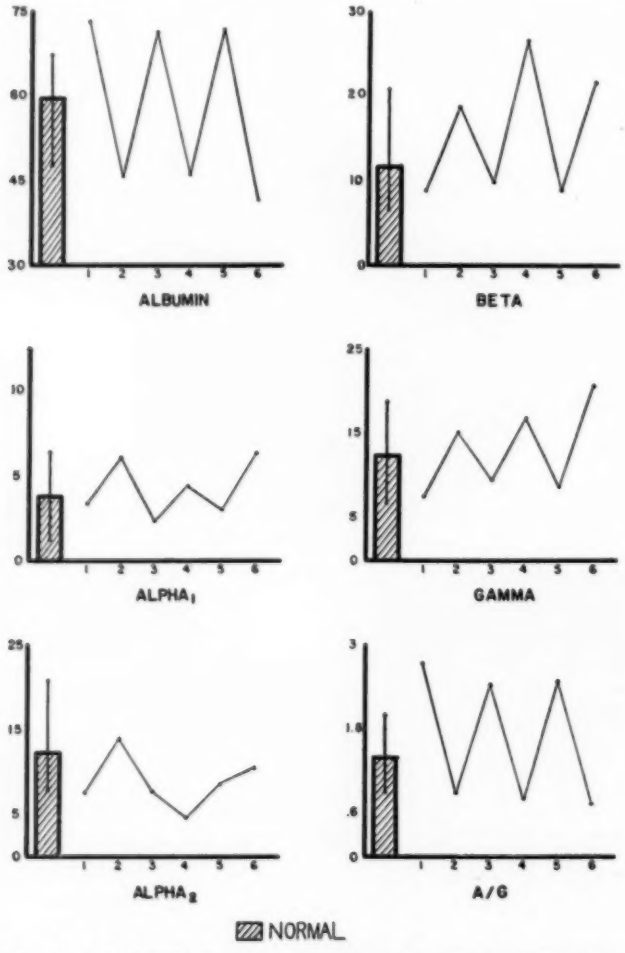

Fig. 8.—Albumin and globulin fractions following various therapeutic regimes. *1*, Initial value; *2*, seven days post cortisone; *3*, post vitamin B_{12} and lipoproteins; *4*, post ACTH; *5*, seven days post vitamin A; *6*, post antibiotics.

this fraction, significant increase of the beta fraction, and significant increase of the gamma fraction. Vitamin B_{12} plus lipoproteins (choline and methionine) and vitamin A have no B_{12} and lipoproteins (choline and methionine).

Table II indicates the values for the various lipoprotein fractions, and for convenience the beta and gamma

lipoprotein values have been combined, since they apparently respond similarly. Figs. 9 and 10 and Table II indicate that under all regimes of therapy, the beta and gamma lipoprotein levels were significantly high when compared to the normal values and were apparently unaltered from the initial determinations. The alpha fractions were correspondingly decreased. Cortisone seemed to increase the beta and gamma levels and lower the alpha fraction even further, but, in general, therapy seemed to be ineffective against the high levels of beta and gamma lipoproteins.

Table III indicates the ranges of varying blood elements and corresponding levels in the child. The hemoglobin, red blood cells, lympho-

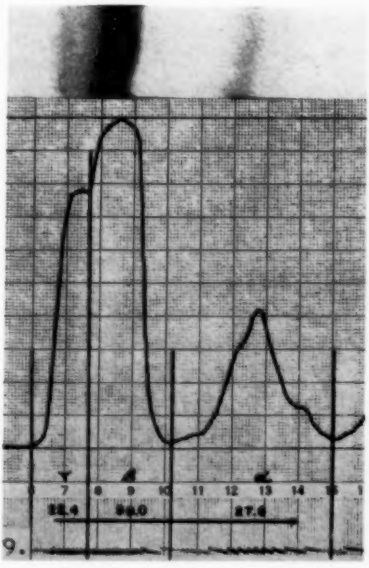

Fig. 9.

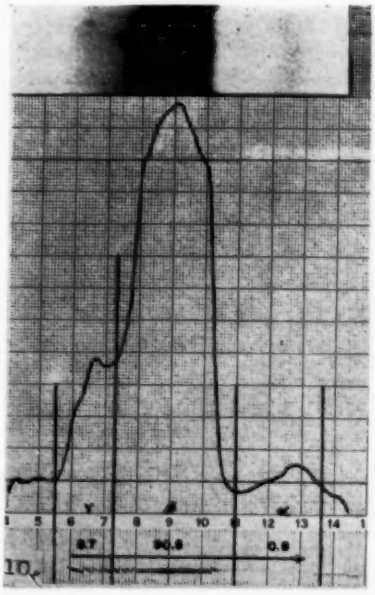

Fig. 10.

Figs. 9 and 10.—Electrophoretic patterns and curves for lipoproteins. *9*, Normal curve. *10*, Curve and pattern representative of all stages of therapeutic regimes (all were essentially alike).

TABLE II. PAPER ELECTROPHORESIS. SERUM LIPOPROTEINS

TREATMENT	ALPHA (%)	BETA + GAMMA (%)
Normal	20-40	60-80
Initial	3.8	96.2
7 days post cortisone	0.8	99.2
Post B_{12} and lipoproteins	2.8	97.2
Post ACTH	6.1	93.9
7 days post vitamin A	2.5	97.5
Post antibiotics	1.4	98.6

cytes, and neutrophils were unchanged in the over-all picture when compared to the initial value and usually fell within the normal range, though being at either extreme at various times. The white blood cells were initially high and rose to a higher level under therapy. The reticulocytes were initially high and maintained their high levels. The platelets were also

initially within the normal range but at a very low normal and then seemed to drop, apparently more related to the development of the disease than correlated with the respective therapy.

Table IV indicates ranges for blood Na, K, Cl, and urea and corresponding levels in the child. Initially, the Na level fell within the normal limits, but the K, Cl, and urea levels were slightly below normal, although not too significantly. Under therapy, the Na maintained normal levels except for a slight decrease with cortisone; K remained just slightly below normal except with antibiotics; Cl levels returned to normal and fell within range; and urea was increased with cortisone, with B_{12} and lipoproteins, and with vitamin A, above normal, whereas ACTH and antibiotics raised the level above the initial value, but still not sufficiently to reach normal values. It can be stated that on an over-all examination of the data, except for the rise of urea levels to 42.0 under cortisone, 42.5 with B_{12} and lipoproteins, and 40.5 under vitamin A, the Na, K, and Cl, as well as urea values, are all relatively normal.

Table V indicates the levels of serum (total) cholesterol and serum cholesterol esters and indicates that the initial values for both were slightly above normal, corresponding to the lipoprotein findings. The levels were brought within the normal range with therapy, except for ACTH, under whose regime they were further ele-

TABLE III. PERIPHERAL BLOOD

TREATMENT	Hb (GM. %)	RBC'S (10^6)	WBC'S (10^3)	RETICS (%)	LYMPHS (%)	NEUTS (%)	PLATELETS (10^3)
Normal	12-14 (76-90%)	4.3-6.0	5.0-10	0-1.0	20-40	0-60	200-500
Initial	12.3 (79%)	4.35	10.9	3.1	39	51	215
7 days post cortisone	8.7 (56%)	3.02	37.0	2.7	35	34	150
Post B_{12} and lipoproteins	11.7 (75%)	3.90	26.8	6.1	26	70	160
Post ACTH	12.2 (78%)	4.00	16.2	3.7	33	55	180
7 days post vitamin A	13.3 (85%)	4.50	20.3	2.7	36	54	150
Post antibiotics	11.7 (75%)	3.78	41.0	3.4	30	60	90

TABLE IV

TREATMENT	Na (MG. %)	K (MG. %)	Cl (MG. %)	UREA (MG. %)
Normal	310-340	18-22	350-390	25-35
Initial	322	17.6	329	17.3
7 days post cortisone	306	16.6	354	42.0
Post B_{12} and lipoproteins	337	17.6	354	42.5
Post ACTH	317	14.1	378	20.3
7 days post vitamin A	322	15.8	354	40.5
Post antibiotics	334	19.2	373	23.5

TABLE V. CHOLESTEROL DETERMINATIONS

TREATMENT	SERUM CHOLESTEROL (TOTAL—MG. %)	SERUM CHOLESTEROL (ESTERS—MG. %)
Normal	110-300	75-210
Initial	311	235
7 days post cortisone	269	164
Post B_{12} and lipoproteins	269	196
Post ACTH	344	281
7 days post vitamin A	200	134
Post antibiotics	207	170

vated. One notes, however, that though the levels do fall within normal ranges, they do nevertheless remain near the high end of the scale.

DISCUSSION

The simultaneous application of electrophoretic studies with the administration of varying therapeutic agents has only recently been attempted in an effort to characterize specific diseases with the varying protein and lipoprotein components. These attempts, due to the fact that the serum proteins are nonstatic entities, have shown some promise in regard to such diseases as nephrosis, hypertension, diabetes, xanthomas, and atherosclerosis, to cite a few.[9] However, limitations in our present knowledge of serum proteins and lipoproteins preclude the possibility of explaining all the variable changes that occur, and we can only speculate and present the existing data.

The use of cortisone and ACTH in the treatment of a great variety of diseases has been widespread, and the results have been just as variable. White and Dougherty[10, 11] have shown that injection of adrenocorticotropic hormone in the intact animal induces lymphopenia and a simultaneous rise in the beta and gamma globulins which have been definitely linked to the production of antibodies. According to Lewis and Page,[12] an increase in the beta globulin concentration is largely accounted for by an increased concentration of lipoprotein associated with vascular changes. Thus, the pituitary adrenotropic hormone seems to control the rate of release of serum globulins from lymphoid tissue. Bossak and associates,[13] on administration of cortisone in dogs, found a selective elevation of the alpha$_2$ fraction associated with a drop in the beta globulin fraction, with no hypoalbuminemia or total protein change and no real change in the lipoproteins. Mason and coworkers[14] demonstrated no change in either quality or quantity of the serum protein on the administration of ACTH to normal human subjects, and Winter[15] produced reversible hyperadrenocortinism in rats by prolonged administration of cortisone. In our experiment, cortisone, ACTH, and antibiotics all lowered the albumin fraction, raised the alpha fractions (except for an unexplainable drop in the alpha$_2$ fraction with ACTH), and greatly elevated both the beta and gamma globulins. The lipoproteins were apparently unaffected by the use of the above therapy. The rise in beta and gamma globulin fractions is in accord with the work of White and Dougherty,[10, 11] except for the lack of any lymphopenia. To further complicate the issue, it has been demonstrated that destruction of lymphoid tissue may in many instances give rise to decreased production of antibodies, whereas stimulation may increase it.[16-18]

One cannot explain the true significance of the rise of the beta and gamma fractions at present. Reports in the literature are conflicting with respect to the effect of ACTH and cortisone on the two fractions. In animal experiments, the hormones cause a significant increase in the total serum globulins, due primarily to an increase of the beta and gamma fractions. In the human being, the effect of gamma globulin is not the same and the effects are variable, the alterations being due to therapy and the clinical course of specific diseases.

The $alpha_2$ globulin has been correlated with the mucoprotein tyrosine, and here may be found the serum mucoproteins. In cases of rheumatic fever[19, 20] and in acute disseminated lupus erythematosus,[21] ACTH and cortisone have no effect on the $alpha_2$ or the mucoprotein tyrosine. However, Bossak and colleagues[22] indicate that, in dogs, a selective $alpha_2$ elevation on daily cortisone injections is seen. In our case, the alpha fractions were elevated with cortisone, ACTH, and antibiotics, when compared to the initial values found, but never moved beyond the so-called normal range after the therapy was given.

Vitamin B_{12}, vitamin A, and lipoproteins seemed to have no effect upon the protein picture or peripheral blood picture.

The administration of all therapy had little effect upon the general peripheral blood picture except for an apparent elevation of the white blood counts, probably due to antibody formation. The Na, K, Cl, and cholesterol values were not altered markedly, and even the rise in urea can probably be explained on the basis of the clinical course of the disease rather than on the respective therapy used.

The failure of the lipoprotein fractions to be affected by the therapy used is of great significance, particularly since this is a disease of lipoidosis. Since these fractions are linked with the beta and gamma globulin fractions, it is difficult to explain their low levels initially and during stages in the therapy with the very high levels of the beta and gamma lipoproteins. These are the fractions that must be moved in order to change the progress of the disease. The shifting of the protein fractions with the therapy used may be an indication of future possibilities, but their true significance is still unknown. However, since the lipoproteins were apparently unaffected, it must be assumed that factors other than the hormones of the adrenal cortex are involved in the disease.

SUMMARY

1. Cortisone, ACTH, and antibiotics (Mysteclin, streptomycin, Terramycin, and Chloromycetin) lowered the A/G ratio, with a respective lowering of the albumin fraction and subsequent increases of the $alpha_1$, $alpha_2$, beta, and gamma fractions, the greatest increase being in the beta and gamma fractions.

2. Neither vitamin A nor B_{12} and lipoproteins (choline and methionine) had any effect on the protein fractions.

3. The therapy used had no significant effect on the peripheral blood picture, Na, Cl, K, urea, or cholesterol levels, outside of variable changes that were undoubtedly due to the clinical manifestations of the disease rather than the therapy used.

4. The therapy failed to affect the all-important lipoprotein fractions which are so significant and essential in a disease of the lipoid type.

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Of Fallyng of the Fundament

Many times it happeneth that the gut called of the latines rectum intestinum, falleth out at the foundament, and can not be gotten in agayne without peine and labour, whiche dysease is a common thyng in chyldren coming oftentimes of a sodaine colde or a long laxe, and may well be cured by these subscribed medicines.

If the gutte hath bene long out, and be so swollen that it cannot be reposed, or by coldnes of the ayre be congeled, the best counsell is to let the chylde sit on a hote bathe, made of the decoction of mallowes, holyhocke, lyneseede, and the rootes of lylyes, wherin you shall bathe the foundament with a softe cloute, or a sponge, and whan the place is suppled thruste it in agayne, which done, than make a pouder thus

A pouder for falling of the fundament.

Take the pouder of an hartes horne brent, the cuppes of acornes dried, rose leaves dried, goates clawes brent, the rinde of a pomegranate, and of galles, of everye one a porcion. Make them in pouder, and strowe it on the fundament. It shal be the better if you put a lytle on the gut, afore it be reposed in the place, & after it be setled, to put more of it upon the fundament, than binde it in with hote linnen clothes, and gyve the childe quinces or a rosted warden, to eate with cinamone and suger.

From Thomas Phaire: The Boke of Chyldren, 1544.

FREQUENCY OF CEREBRAL LATERAL DOMINANCE VARIATIONS AMONG SCHOOL CHILDREN OF PREMATURE AND FULL-TERM BIRTH

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THIS study of birth weight and cerebral lateral dominance (or sidedness) was made in connection with a long-term investigation of the effects of premature birth on children of school age. Previous findings are at variance with the commonly held belief that the handicap of premature birth is largely overcome by the time a child is ready to enter school.

An early report showed more neurological lesions, defective vision, slow speeds of visual perception, certain lateral dominance variations, and a higher incidence of reading failure among children of premature birth than in a nonpremature group of school children.[1]

A later study compared 155 children of school ages who weighed 5.5 pounds or less at birth with 439 of comparable ages with birth weights over 5.5 pounds (considered full term). The findings disclosed a higher percentage of vision below 20/20 among the premature subjects and a higher "average" (median) degree of subnormal vision at all ages from 5 through 9 years.[2]

Further investigation revealed a tendency for birth weight, visual acuity, and the speeds of object and word perception to exhibit a higher correspondence in a group whose members weighed less than 5.5 pounds at birth than among those whose birth weights were over 5.5 pounds.[3]

The present study was made because of the controversial position of lateral cerebral dominance of eye and hand in the etiology, diagnosis, and treatment of language disabilities, particularly in the fields of speech, reading, writing, and spelling. For example, it is often alleged that lateral cerebral dominance variations (such as dominance of the nonpreferred hand, uncertain dominance, or confused dominance) are likely to be associated with speech difficulties, particularly with delayed speech and stuttering, while sinistrality has been blamed for reversal tendencies in reading and writing, in which "b" becomes "d," "saw"—"was," and "dog"—"god," as well as the tendency to try to read from right to left.

Confused and uncertain dominance of both eye and hand or either have been coupled with reading, writing, and spelling failure as an explanation of such common errors as reversals, regressions, confusions, defects of orientation, and the like.

Some believe that lateral cerebral dominance variations produce language difficulties through defective integration in the dominant half of the cortex as a result of some dysfunction of the thalamus, cerebellum, or the nondominant hemisphere.[4]

Five hundred case records were reviewed, of which fifty-three were disqualified because of questionable test results or recording, leaving 447 cases. Forty-three of them (9.6 per cent) had birth weights of 5.5 pounds or less (premature group) and 404 had birth weights of more than 5.5 pounds. The age range was from 5 through 17 years.

Each child in the study had been given ring and aiming tests of eyedness, and throwing and reaching tests of handedness. Other, supplementary tests of both eyedness and handedness were used in almost every case, although there was some variation in the number of supplementary tests used and in the selection of those which were used as supplements.

The categories of cerebral lateral dominance studied included the following: right eyedness with right handedness (deemed normal), left eyedness with left handedness, right eyedness with left handedness, left eyedness with right handedness, amphiocularity with right handedness, amphiocularity with left handedness, right eyedness with ambidexterity, left eyedness with ambidexterity, and amphiocularity with ambidexterity.

The cases falling in each of the categories were distributed by birth weight, and the frequency of each combination of cerebral lateral dominance was determined and recorded. The entire group was subdivided at the 5.5 pound birth weight line, with those with birth weights of 5.5 pounds or less forming the "premature" group and the others the "full-term" group.

A comparison of the frequency of each of the cerebral lateral dominance variations in these two groups showed 20 per cent more of the combinations *other than* right eyedness with right handedness among the "premature" group, the frequency of such variations being 74 per cent among the "prematures" and 54 per cent among the "full terms."

It is sometimes argued that left eyedness with left handedness is really a normal situation to the extent that both eyedness and handedness controls are on the same side of the brain. With this in mind, the frequency of combinations *other than* right eyedness with right handedness *and* left eyedness with left handedness was determined.

The "premature" group exhibited 10 per cent more of these variations, their frequency being 57 per cent, while that of the "full terms" was 47 per cent.

Although it is possible that we should regard left eyedness with left handedness as "normal," it should be pointed out that this condition is opposed (in theory at least) to the left-to-right approach to reading, writing, and spelling which is characteristic of our culture, and that some have attributed mirror writing and reversals of various kinds to extreme sinistrality.

I am inclined to feel that left eyedness with left handedness is probably as important as any of the combinations other than right eyedness with right handedness, since it may tend to oppose the cultural tendency.

Further comparison of the two groups revealed that several combinations occurred more frequently among the "prematures"; specifically, left eyedness with left handedness was 10 per cent more frequent there than in the "full-term" groups, left eyedness

with right handedness 8 per cent, amphiocularity with right handedness 8 per cent, amphiocularity with left eyedness 3 per cent, and amphiocularity with ambidexterity 1 per cent.

Conditions occurring less frequently among the "prematures," with the percentage differences, included right eyedness with right handedness 20 per cent less frequent, right eyedness with left handedness 6 per cent, right eyedness with ambidexterity 2 per cent, and left eyedness with ambidexterity 2 per cent.

To the extent that this study is representative, it seems safe to conclude that lateral cerebral dominance variations *other than* right eyedness with right handedness occur more frequently among the "prematures," except for right eyedness with left handedness, right eyedness with ambidexterity, and left eyedness with ambidexterity.

The degree to which variations in lateral cerebral dominance may interfere with language function, the mechanism of such impediment, the frequency of its participation as a factor in the etiology of language failure or defect, and individual differences in response to handicaps of the kind remain to be determined and appear to be a knotty neurological problem.

SUMMARY

Forty-three children between the ages of 5 and 17, whose birth weights were 5.5 pounds or less were compared with 404 of comparable age whose birth weights were over 5.5 pounds. The "premature" group presented 20 per cent more lateral cerebral dominance variations from the "normal" right eyedness with right handedness: higher frequencies of left eyedness with left handedness, left eyedness with right handedness, amphiocularity with right handedness, amphiocularity with left eyedness, and amphiocularity with ambidexterity.

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CONGENITAL LEUKEMIA ASSOCIATED WITH MONGOLISM

Report of a Case

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THERE is still little known about the cause of leukemia. More attention is being given to the coexistence of leukemia with various diseases and with developmental defects. The interesting association of leukemia and mongolism in children has been the subject of two recent reports. Krivit and Good[1] have reported five cases, and Merrit and Harris[2] reported four cases. In 1930, Brewster and Cannon[3] reported a case of acute leukemia in an 11-month-old mongoloid boy. Ingalls,[4] in discussing the pathogenesis of mongolism, cited two mongoloid children who died of acute leukemia. Bernhard and associates[5] presented data on fourteen cases of congenital leukemia, one of which occurred in a newborn male mongoloid infant. Schunk and Lehman[6] reported two newborn infants with mongolism and congenital leukemia; however, one of these infants was alive four years later and had a normal bone marrow. O'Conner and co-workers[7] reported a mongoloid male infant who died on the fifth day of life with a diagnosis of acute myelogenous leukemia. The presence of a hemolytic streptococcic septicemia in this last case throws some doubt on the diagnosis of leukemia, as it is known that severe infection in young infants can produce a leukemoid reaction.

From the Driscoll Foundation Children's Hospital.

CASE REPORT

A 4-day-old male infant of Mexican parentage was admitted to the hospital on Feb. 20, 1956, because of bleeding from the urethral meatus. The delivery had been normal. The infant weighed 4,080 grams at birth. On the third day, a small amount of fresh blood was seen dripping from the urethral meatus. This bleeding continued intermittently to the time of admission.

The parents and five siblings were in good health. Serologic tests for syphilis were negative in both parents. The mother, aged 39 years, was type O, Rh positive. Her pregnancy had been uneventful.

Physical examination on admission showed a male infant 53 centimeters in length and 3,895 grams in weight. The infant had quite definite features of mongolism (Fig. 1), including epicanthal folds, flat nose, prominent and pudgy appearance of the back of neck, and generalized hypotonicity. The lower edge of the liver was palpable 3 cm. and that of the spleen 4 cm. below the costal margins. The umbilical stump appeared moist. Fresh blood dripped from the urethral meatus during the examination. A harsh systolic murmur was heard along the left sternal border.

The leukocyte count on admission was 90,000 per cubic millimeter, with 3 per cent neutrophils and 97 per cent immature lymphocytes. The erythrocyte count was 5,640,000 per cubic millimeter, and hemoglobin 18 grams per 100 ml. The platelet count was 20,000 per cubic millimeter. Bleeding time was 20 minutes, coagulation time

12 minutes (Lee and White), and prothrombin time 18 seconds (control, 15 seconds). Blood type was group O, Rh positive. The Coombs test and test for syphilis were negative. Blood and spinal fluid cultures were negative. Cultures from the umbilicus were positive for *Staphylococcus aureus* hemolyticus. The urine was grossly bloody. Subsequent leukocyte counts during the hospital course ranged between 80,000 and 160,000 per cubic millimeter, and the platelet counts from 20,000 to 40,000. Sternal bone marrow smears revealed 26 per cent stem cells, 2 per cent myelocytes, 1 per cent band cells, 4 per cent segmented neutrophils, and 67 per cent immature lymphocytes. There were few megakaryocytes and platelets. The cytomorphology was compatible with acute lymphatic leukemia.

The infant's condition deteriorated rapidly. A few days after admission, the abdomen became markedly distended, and the infant became dyspneic and cyanotic. Crepitant râles appeared in both lungs. There were frequent episodes of epistaxis. The bleeding from the urinary tract continued intermittently throughout the hospital course. Antibiotics were given during the entire period; and corticotropin, 40 U. daily, was given for the seven days preceding death. The infant died on March 7, 1956, at 16 days of age.

Upon autopsy the facies was found to be typically mongoloid. Grossly, the skin showed generalized pitting edema. The lymph nodes in the neck, axillae, and inguinal regions were enlarged. Blood was present in the nares, mouth, and about the anal orifice. The subcutaneous tissues were thick, pseudogelatinous in appearance, and flecked with petechial hemorrhages. The liver was large, purplish red, and weighed 198 grams. The spleen was firm and hemorrhagic. It weighed 50 grams. The rib marrow was thick, pulpy, and hemorrhagic. The thymus gland was large and fleshy, with numerous hemorrhagic areas. The heart weighed 45 grams. It showed a patent foramen ovale and an inter-ventricular septal defect. The lungs were edematous, and cut sections showed diffuse hemorrhagic extravasation. The lymph nodes in the chest and abdomen formed large clusters of soft, hemorrhagic masses up to 2 cm. in diameter. Microscopic sections of the thymus, heart, lungs, liver, spleen, and lymph nodes all showed extensive infiltration with immature lymphocytes. The bone marrow was markedly cellular and consisted almost entirely of immature cells having the morphologic characteristics of lymphoblasts.

Fig. 1.—Note the drops of blood on the right thigh from urethral bleeding.

COMMENT

The true incidence of mongolism associated with leukemia is probably

higher than the several reports would indicate.[1, 8, 9] Mongolism cannot always be recognized during the neonatal period,[10] and may thus be missed before the infant succumbs to acute leukemia.

If further investigation bears out the opinion of Krivit and Good[1] that simultaneous occurrence of leukemia and mongolism cannot be explained by probability alone, the question of how these two conditions are related is an interesting speculation.

The various defects of different organs involved in mongolism strongly suggest injury to the fetus between the sixth and ninth weeks of fetal life.[4, 11] It is reasonable to assume that the hematopoetic system may be injured simultaneously and that leukemia is the result of this same insult. However, it is also quite possible that mongolism predisposes to the occurrence of leukemia and that they do not result from the same injurious prenatal cause. In almost half of the reported cases, the time of manifestation of leukemia varied anywhere from 2 to 10 years of age. It would seem that if both conditions were produced by the same intrauterine insult there should not be such a long interval between birth and the onset of leukemia.

SUMMARY

The clinical and pathological findings of a case of mongolism associated with acute lymphatic leukemia in a newborn male infant is reported. The relation between the two conditions is briefly discussed.

Dr. Joseph G. Pasternack performed the pathological examinations.

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ANHIDROTIC ECTODERMAL DYSPLASIA WITH VASCULAR PURPURA

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CONGENITAL anhidrotic ectodermal dysplasia is a rare hereditary condition in which there is marked underdevelopment or absence of the structures derived from the embryonic ectoderm. There are three main features of the syndrome: first, and most important, a complete or nearly complete absence of the sweat glands which results in marked impairment of the heat dissipation mechanism of the body; second, a partial or complete absence of the teeth, and third, the sparse scalp and body hair of a fine brittle texture.

This condition occurs far more frequently in males, with a sex ratio of five to one.[1, 2] Most of the patients described in the literature have a family history of similar defects, and a definite sex-linked recessive inheritance has been described in some pedigrees.[3, 4] Other modes of genetic transmission seemed likely in other families.[5, 6] Approximately eighty cases had been described prior to 1947,[1, 2] and another score have been reported since.

This report describes a male child with congenital anhidrotic ectodermal dysplasia who was studied because of a petechial rash, which proved to be a nonthrombocytopenic vascular purpura.

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The opinions or assertions contained in this article are the private ones of the writers and are not to be construed as official, or reflecting those of the Navy Department or the Naval Service at large.

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CASE REPORT

M. C., a 15-month-old white male, was admitted to the United States Naval Hospital, Bethesda, Md., on June 28, 1956, for evaluation of a petechial eruption. Pregnancy and delivery were normal. The mother's serologic test for syphilis was negative. A younger brother had developed normally. The mother's dentition was delayed; her first tooth had erupted at age 2. Dental roentgenograms when she was 15 years old showed only twenty-four teeth.

FIG. 1.—Anodontia and marked hypoplasia of the gums.

The upper central incisors were malformed, cone shaped, and had poor enamel structure, requiring extraction at age 15. Her eyebrows were deficient on the lateral aspects, and her axillary and pubic hair was sparse. The left mammary gland was underdeveloped, being only a flat areola. No enlargement of this breast had occurred during pregnancy and lactation, although the right breast had reacted normally. Her nails were normal, and she perspired freely when hot. No other family history of ectodermal defects could be elicited.

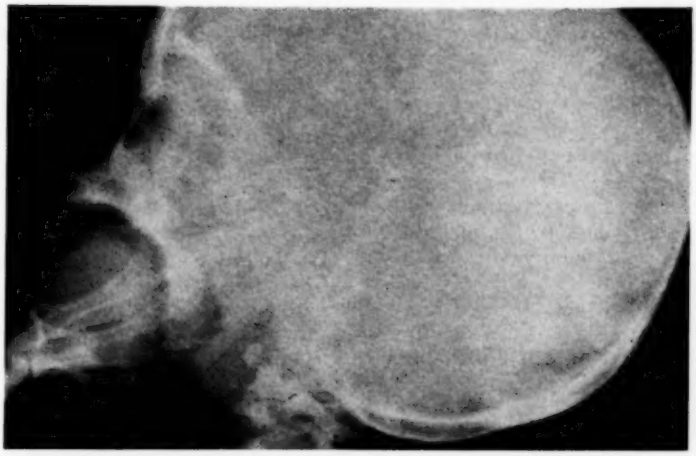

Fig. 2.—Lateral roentgenogram of the skull demonstrating mandibular anodontia and only two unerupted molars in the maxilla.

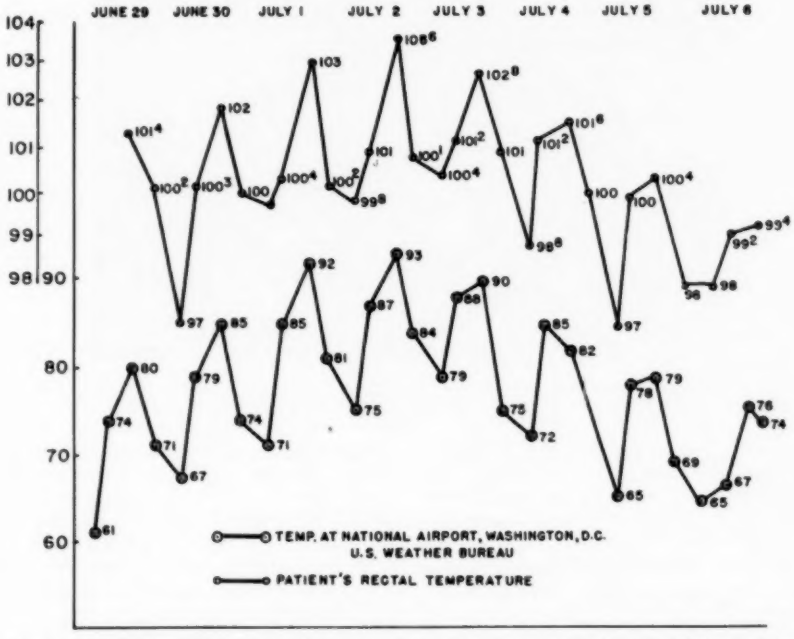

Fig. 3.—Patient's temperature chart compared with the local environmental temperature

The child appeared to develop normally during the first months of infancy. However, episodes of fever, irritability, and listlessness had occurred. The mother had noticed a few petechiae on the child's skin during the first year of life, but during the three months before admission these had greatly increased in number. Supplementary vitamin C had been given from 2 weeks of age. No other drugs or medications had been administered.

The child was very irritable and appeared pale. His facial configuration suggested that of a little old man. The hair was scanty and white, and no eyebrows were present. The bridge of the nose was flattened, and there was a purulent nasal discharge. No teeth had erupted; the alveolar ridges were markedly underdeveloped (Fig. 1). The nipples were present. The skin was very white and dry; it was quite stretchable and had an elastic quality. Scattered over the skin of the extremities and body were many petechiae.

Roentgenograms showed normal bony structure and ossification centers. Lateral views of the skull showed mandibular anodontia. Two unerupted molars were present in the maxilla (Fig. 2). A complete blood count and urinalysis were normal. The serologic test for syphilis was normal.

The platelet count was 330,000 per milliliter. The bleeding time by the Ivy technique was five minutes. The Lee-White clotting time was seven minutes. Prothrombin time and prothrombin consumption were normal. Bone marrow studies showed no abnormality; normal megakaryocytes were present. The tourniquet test was positive, thirty-five petechiae appearing in a 2.5 cm. area after six minutes of 60 mm. Hg pressure.

A daily temperature elevation was recorded, but no localizing findings of infection could be found and the blood cultures were sterile. The temperature chart is reproduced in Fig. 3 and is compared with the local environmental temperature as recorded

Fig. 4.—Skin biopsy from the axilla. No sweat glands or coil ducts are seen. The hair follicles and sebaceous glands are small and underdeveloped.

by the United States Weather Bureau. No cutaneous sweating was noted even when the patient's temperature was the highest.

An axillary skin biopsy was performed, and no sweat glands were noted on serial sections of the specimen. The pilosebaceous structures were small and underdeveloped (Fig. 4). Elastic tissue stains showed some decrease in the number and fragmentation of the dermal elastic fibers. The capillaries appeared normal.

The child was given 200 mg. of rutin and 100 mg. of ascorbic acid a day, and the petechiae decreased in numbers. Two months later the tourniquet test produced only five petechiae and only a few were noted on the skin.

Adequate sponging, followed by the use of an electric fan, has controlled the child's hyperthermia. Dentures will be fitted at the earliest possible time.

DISCUSSION

The association of vascular purpura with anhidrotic ectodermal dysplasia in this case is unique. Recently Koszewski and Hubbard[7] described a 22-year-old man who had congenital ectodermal defects, including hypotrichosis and faulty dentition. Associated in this case was a chronic anemia and vascular purpura. However, their patient had normal sweat glands, only "slightly decreased" in numbers, and apparently did not have the physiognomy which is characteristic of the anhidrotic or major variety of ectodermal dysplasia as described by Weech.[8]

The fragmentation and decrease in numbers of the dermal elastic fibers seen in our case have been described in other patients.[9, 10] Similar but more extensive changes are also seen in the Ehlers-Danlos syndrome, and vascular purpura is frequently seen in this hereditary condition.[11] A primary abnormality of the capillary walls could also have been present and this might be in accord with the apparent remission of the purpura after the administration of ascorbic acid and rutin.

SUMMARY

A case of congenital anhidrotic ectodermal dysplasia is presented. The case is of special interest in that the child also had a nonthrombocytopenic vascular purpura.

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CONSTANT INFUSION PUMP FOR LIMITING FLUIDS

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MANY times the pediatrician is faced with the problem of giving intravenous fluids, but, because of singular situations, he wants to limit the amount to very small quantities. This is particularly true when dealing with premature and newborn infants, postoperative patients, infants with congenital heart disease, and when it is necessary to keep an intravenous route available for medications and emergency use in older children in congestive failure. When fluids run too slowly into a vein or cut-down, thromboses frequently occur, so that the fluids stop. At other times, even though fluids are checked, disastrous amounts suddenly run into a patient. For these reasons a machine was developed which would safely deliver definite known small quantities of fluids.

The machine is an aluminum, "lathe-like" apparatus which slowly empties a large syringe. It weighs 2.5 kg., measures 46 cm., and easily sits on a bedside table. With proper gearing, almost any desired volume of fluid can be delivered. For our purposes, the machine was geared to deliver four different quantities ranging from 114 ml. per twenty-four hours (1.2 drops per minute) to 240 ml. per twenty-four hours (2.5 drops per minute).

In Fig. 1, abbreviated plans demonstrate the principle of the machine. A Bodine torque motor (5.7 r.p.m.) is connected to a $\frac{7}{16}$ inch, 14 steel worm gear by the way of a worm and drive gear. The ratio and number of teeth on the drive gears were calculated to move the plunger release (which is the only part of the plunger mounting with a thread) at a rate sufficient to empty a standard 100 ml. syringe in ten hours (240 ml. every twenty-four hours) and a 50 ml. syringe in ten and one-half hours (114 ml. every twenty-four hours). Two different gears had to be used to do this, since the length of a standard 50 ml. syringe is less than that of a 100 ml. syringe. Gears are changed by moving the motor mounting (Figs. 2 and 3) to appropriate holes in the plastic sheet to which the motor is fastened. This is easily accomplished with screws and wing nuts (Figs. 2 and 3).

By interchanging the syringes with the gears, two intermediate rates can be obtained. A standard syringe filled with the desirable intravenous fluid is placed on the mounting (Fig. 2). The plunger mounting is reset to receive this syringe by squeezing the plunger release (Figs. 1 to 3) and merely pulling it back. The motor is then started and the plunger

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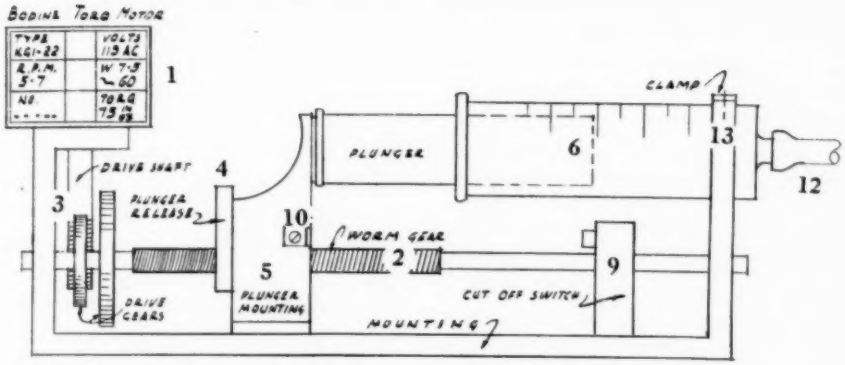

Fig. 1.—Abbreviated plans of constant infusion pump.

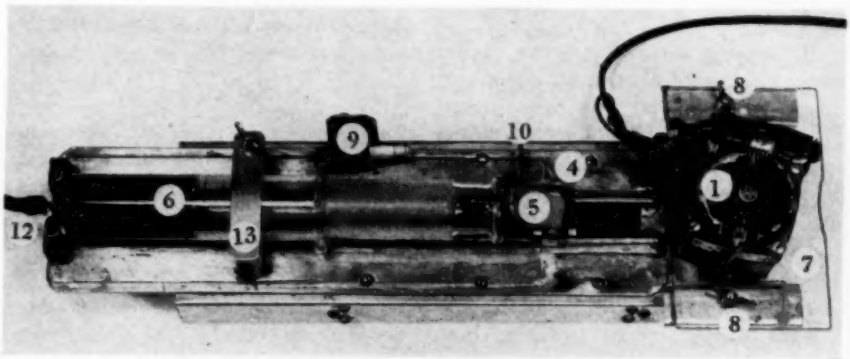

Fig. 2.—Top view of pump.

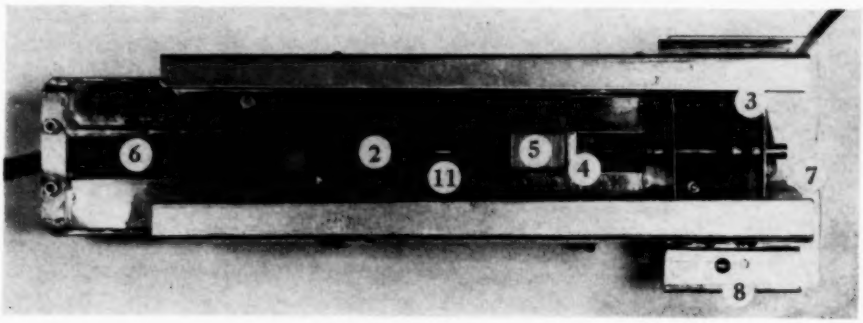

Fig. 3.—Bottom view of pump. *1*, Bodine torque motor, 5.7 r.p.m.; *2*, 7/16 inch, 14 turns per inch steel rod (worm gear); *3*, worm and drive gears; *4*, plunger release; *5*, plunger mounting; *6*, syringe; *7*, plastic motor mounting; *8*, wing nuts holding motor mounting to machine; *9*, cutoff switch; *10*, cutoff switch contact; *11*, bare area on worm gear; *12*, rubber tubing; *13*, clamp to hold syringe.

mounting slowly pushes the syringe plunger and ejects fluid.

Two things were modified in its use so that steadier and more even flow could be obtained:

1. After starting the machine, it should be allowed to run for approximately ten minutes to build up pressure in the rubber tubing and take up inertia in the system.
2. The shaft of the plunger should have one drop of sterile mineral oil put on it and should then be inserted and worked around in the barrel so that there is less friction. The amount of mineral oil used should be limited to one drop to prevent the possibility of oil droplets in the fluid.

Minor adaptations may be made, depending on local circumstances and needs. By altering the gear ratios, larger or smaller amounts of fluids may be delivered. By using different sized syringes (for example, 50 ml., 100 ml., etc.) the range of adaptability of the machine is greatly enhanced. We found that connecting approximately one-half foot of sterile rubber intravenous tubing directly to the syringe before autoclaving was the most practical method of having a "give-set" readily available for use.

There are two safety cutoff devices in order to prevent the syringe from being smashed when it is empty. The first is a switch (Figs. 1 and 2) which is tripped by a projection from the plunger mounting. This automatically cuts off current to the motor. The second is a bare area in the worm gear (Fig. 3) which will not give any push when the thread in the plunger release reaches it.

This machine has now been used for three and one-half years without any complications.

SUMMARY

A machine is described which has been used to give constant small quantities of fluids to infants and older children under a variety of circumstances.

We wish to acknowledge with appreciation the help given by Dimiter Stoyanoff in preparing the drawing for Fig. 1.

CHILD CARE IN RUSSIA

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DURING July, 1956, Dr. Ruth Bakwin and I spent three weeks touring the principal cities of European Russia—Leningrad, Moscow, Stalingrad, Rostov, Odessa, and Kiev. In all these cities we talked to prominent pediatricians and visited children's hospitals and other child care institutions.

It is not easy to obtain information in Russia. Visits to hospitals, outpatient departments, nurseries, and universities must be arranged beforehand through official sources and definite appointments must be made. No great difficulties were encountered until we reached Moscow. There Intourist, the official Russian tourist agency, asserted that it was not its function to arrange hospital visits, that it had to do only with sightseeing; and Voks, the society for cultural relations with foreign countries, took the position that it was concerned only with "culture," and hospitals were not culture. Taunts such as, "Are you, perhaps, ashamed to let us see your hospitals?" and "Shall we go back to America and tell our colleagues that we were not permitted to see your hospitals?" seemed to have no effect.

When, after four days of concentrated effort which was getting us nowhere, the Ministry of Health finally learned of our presence through a fellow American, the gates were opened, and we were given a cordial reception.

A great barrier to getting information in Russia is the evasiveness and, sometimes, downright prevarication of the Russians. They seem to be afraid to say anything which may be interpreted as critical of their system of c h i l d care. All questions are answered by the director who, like directors elsewhere, may not be intimately acquainted with the minutiae of hospital ward practice. Consequently one gets glib answers like, "The death rate from severe diarrhea in babies is one-half per cent." Similarly wild and obviously ridiculous statements are made regarding the small number of premature babies lost.

As an example of the evasiveness of the Russians, in all our visits to Russian hospitals we did not see a single acutely ill child. There are, of course, acutely ill children in Russia as elsewhere. It is obviously not possible for a visitor to see every child in a hospital with several hundred child patients—or to look into every nook and corner. I believe that these children were not shown to us because, in their own distorted way, the Russians regard a sick child as a defeat for their "prophylactic" program which I will describe later.

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For these reasons we have attempted in this account to describe, so far as possible, only what we saw. When we had to rely on what we were "told," that is explicitly stated.

Surprising was the large number of physicians in the various clinics and hospitals. It is not clear how they occupy their time. For example, at an obstetrical hospital where 300 babies are delivered each month there are thirteen obstetricians and three pediatricians. Normal deliveries are managed by midwives. Even if the doctors were to deliver the babies themselves there would be less than one delivery per day per doctor. Prenatal and postnatal visits would be hardly enough to occupy the doctors' time. It is also hard to figure out what three pediatricians do with their time in such a hospital.

Dr. C. Fraser Brockington, professor of social and preventive medicine in the University of Manchester,[1] was similarly impressed by the superabundance of doctors. In a 450-bed maternity hospital which he visited in Tashkent there were seventy-five doctors. Here again there would be less than one delivery per doctor per day.

In the pediatric hospitals and clinics the doctors seemed to "stand around" a great deal. Much time is spent in filling out elaborate hospital records. The hospital charts are voluminous and contain diagrams illustrating the child's hospital course.

Child care is distributed through the district clinics which may or may not be connected with a district hospital. There are no doctors' offices in our sense. The clinics are manned by pediatricians and, in addition, by a group of specialists—ophthalmologists, otolaryngologists, dentists, and others. The clinics are equipped with quartz lamps, high-frequency machines, diathermy machines—apparatus which is of little use in the general treatment of children—and these are proudly demonstrated to the visitor. Children are brought here for check-ups and also when they are sick. If a house call is necessary the parents telephone the clinic or call in person and are told the approximate time when the physician will make the visit. Despite the large number of doctors, appointments at the clinics are not kept rigidly and it is customary to wait about an hour. The patient usually sees the same doctor each time unless he is off duty. The only person with whom I had an opportunity to discuss this told of having four different doctors for his 4-year-old child. Sometimes when the mother comes to see the doctor she may find him surrounded by a group of a dozen or more students.

No charge is made for medical care but the parents must pay for medications.

Doctors work six to six and a half hours a day, two hours less on Saturdays, and they are free on Sundays. A certain number are on call evenings and weekends. Consequently, in case of illness after hours or on weekends, the patients are seen by different doctors.

When the Russian doctors were told that American physicians work about sixty hours or more a week they expressed sincere sympathy for their oppressed and overworked American colleagues.

The Russian pediatricians work, for the most part, like junior hospital interns. Except when making house calls, they work under supervision.

WELL-BABY CARE

The Russians take great pride in their preventive program. This program is, in a general way, similar to that practiced here and in much of the western world.

According to our informants, children are seen monthly during the first year of life but more often during the first three months. Mothers are said to remain in the obstetrical hospital for seven to ten days.

The infant death rate in the large cities, judging from the appearance of the children, is probably low, but in the absence of accurate data it is easy to be misled. According to Dr. Brockington, who visited Russia in the fall of 1955, "the diet for both adults and children is almost certainly low in protein and there seem to be no measures of priority feeding." Presumably by "priority feedings" he refers to special food allowances for pregnant women, children, and so on. It is not possible to make any estimate of rural death rates since foreigners are not permitted to visit villages.

With few exceptions babies in Russia are breast-fed. This applies to the professional groups as well as to the laboring classes. Babies are still fed every three hours, and women are given time off from their work to go to the factory nursery to nurse their babies.

Babies are still swaddled. The Russians use three layers of swaddling cloth under which the baby wears a shirt and diaper. Although the babies are swaddled tightly, they seem quite comfortable and contented.

Prophylactic inoculations are given against smallpox, diphtheria, and tuberculosis. Inoculations against tetanus are not given in Russia because, we were told, "there is no lockjaw in the U.S.S.R.," an obvious absurdity.

Poliomyelitis is uncommon in Russia. A small epidemic occurred in Stalingrad in 1954, and as hygiene improves it will probably become an important problem there as elsewhere. Russian doctors showed no curiosity regarding American pediatrics and never volunteered questions. When we offered to answer any queries which they might have, they asked only about the Salk vaccine.

Vitamins are given to all infants and great reliance is placed on them. Thus we were told in Leningrad that children with pneumonia are treated with penicillin and "vitamins." The vitamins used are vitamin C, niacin, and "vitamin B." These are given "to increase resistance to infection."

Check-ups are continued throughout childhood, but it was not possible to find out at what intervals.

When we asked what is done about mothers who fail to come back regularly for check-ups we were told that they always return.

Although categorically denied by some physicians of whom we made inquiry, there is a certain amount of private practice in Russia. One father told of a consultation regarding the advisability of tonsillectomy for his child for which a fee of 100 rubles* was paid. Some persons, impatient with the time required in going to the clinic to make an appointment, the inconvenience of the hour of the appoint-

*The official rate of exchange is 25 cents for a ruble. At this rate a pair of shoes costs approximately $100, an embroidered shirt $100, the cheapest man's shirt $20, a man's suit over $200, and a child's cotton dress $25 to $40.

ment, the waiting, and the lack of privacy, prefer to pay a doctor to be seen in private.

TRAINING OF THE PEDIATRICIAN

The medical course in Russia lasts six years. The average age at entry to medical school is 17 years. The classes are very large—700 at the First Moscow Medical Institute. It is hard to see how such large numbers of students can receive the individual instruction which we consider necessary for the proper training of a doctor. Moreover, immense numbers of sick patients would be necessary if the students were to have sufficient clinical material.

Training for the specialty of pediatrics begins in the third year at medical school and continues until graduation at 23 years, when the physicians are considered to be qualified pediatricians.

The number of physicians graduated each year in Russia is enormous. In the R.S.F.S.R. which includes about 110,000,000 out of a total population of 200,000,000 in U.S.S.R., 2,000 to 2,500 "pediatricians" are graduated each year. Leningrad alone, one of the fourteen schools in the R.S.F.S.R. which has a pediatric "institute," graduates about 330 a year. In all of the United States there are about 6,000 properly qualified pediatricians.

During their training, students receive an allowance from the government which is meager but seemingly adequate.

On graduation, the physician is assigned to practice in a designated area. A certain amount of choice is given—he may select one of five or six locations. The salary on graduation is 800 rubles per month. (Our chauffeur's salary was 1,300 rubles plus bonuses for using little gasoline, for keeping down car repairs, and so on.) The salary is increased every two or three years so that a physician ten years after graduation receives about 2,000 rubles monthly. A few of the top professors receive 6,000 rubles.

A certain number of physicians return later on for advanced training.

Pediatries is the most popular of all the specialties. It is chosen by 30 per cent or more of all the medical students. Psychiatry is the least popular of the major specialties. There is much less interest in child psychiatry than here in the States.

Fully 90 per cent of the pediatricians in Russia are women. However, most of the leading pediatricians are men. A notable exception is Professor Olga Sokolovna of Moscow who bears the title of Academician—the highest scientific title in Russia. Many of the hospital directors and public health officials are women. The principal pediatricians are, for the most part, of an age indicating that they were trained before the Revolution or in the twenties.

HOSPITALS

The children's hospitals in Russia are housed in very poor buildings. In none of the cities that we visited did we see a hospital that looked as though it had been built after the Revolution. Some are probably converted homes. The large hospitals consist of a number of separate buildings for different diseases—rheumatic fever, contagious diseases, infants' diseases, tuberculosis, and so on. The larger hospitals are generally surrounded by extensive parks with beautiful, well-kept flower

gardens and play areas for the children who are well enough to go outdoors.

Permission to visit a hospital must be arranged beforehand. The visit is made under the guidance of the hospital director or his assistant and questions are answered by him. The visitor is clothed in cap and gown; sometimes the wearing of masks is also required. Little effort is made to give the hospital an informal air. Although murals and toys are occasionally used, one misses the colorful window hangings and the gay furnishings which have become essential features of the modern American children's hospital. Old-fashioned glass cubicles are still widely used for the babies.

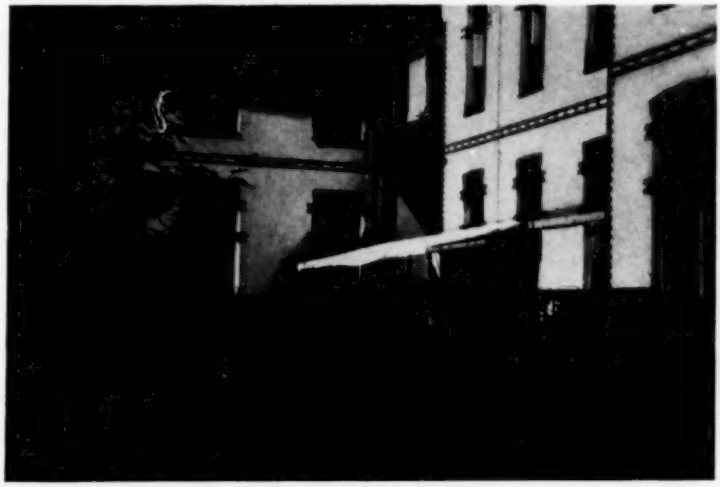

Fig. 1.—The Children's Hospital in Leningrad.

When we asked in each city to see the "best" children's hospital we were told that all were of the same high caliber, the inference being that a program of child care has been put into operation which functions without regard to the qualities of the persons who run it.

In most of the hospitals which we visited, free visiting by parents was permitted.

The wards are clean and free from flies and smells. The beds are closer together than in most American hospitals. The nurses lack the trim, efficient appearance of the American nurses but they impress one as warm and motherly and kind. Many of the beds are occupied by children with minor illnesses—colds, stomach and intestinal upsets, acute hepatitis—cases which are not ordinarily admitted to American hospitals. There are several reasons for having these children in the hospital: most of the mothers work and consequently there is no one to look after a child—well or sick—at home. The homes are tiny and crowded. The poorly trained physicians can hardly be expected to distinguish a really sick from a well child and, consequently,

where the least doubt exists, send the child into the hospital.

When a physician makes a visit to a strange hospital, it is customary to show him unusual or rare diseases, difficult diagnostic problems, and newly discovered syndromes. During our visits to hospitals in the various cities we saw none of these. Instead the visits consisted of a walk through the wards, in the course of which we asked questions about the nature of the illnesses and their treatment. Consequently it was not possible to gauge the knowledge of the Russians. By and large, treatment follows the lines used here and elsewhere in the western world. Most of the antibiotics available here—penicillin, streptomycin, Aureomycin, Chloromycetin—were found there—bearing Russian labels.

We saw a great many children with rheumatic fever. Rheumatic fever prophylaxis is not used.

When we asked about cardiac surgery in Leningrad we were told the children were sent for operation to Moscow. In Moscow we were told the patients were sent to Leningrad.

Visitors to the permanent Agricultural Exhibit in Moscow are usually conducted through a pavilion in which is shown Russia's modern medical equipment for x-ray, electroencephalography, electrocardiography, anesthesia, and the like. The equipment is bright and shiny and impressive-looking, but the practicing physician can hardly be expected to judge the quality of manufacture or the newness of design. The apparatus seen at the hospitals was, for the most part, shoddy and antiquated. When we asked when the new equipment was to be put into production the guide's answer was a silent shrug.

Fig. 2.—The Children's Hospital in Moscow in which the beds were crowded.

Dr. Emery Rovenstine, professor of anesthesiology at New York University,

who visited Moscow in August, 1956, found the anesthesia apparatus which was being demonstrated at the Exhibit, presumably Russian manufactured, identical with the one he uses in his own department here. Moreover, the Russian apparatus had an attachment for cyclopropane which is not used in Russia. When he asked about the cyclopropane attachment he was told that it was there in case the use of cyclopropane is adopted later on. Anesthesiology is not regarded as a specialty in Russia.

journal was a copy of the April, 1956, issue of THE JOURNAL OF PEDIATRICS.

VITAL STATISTICS

For some obscure reason vital statistics are a state secret in Russia. No data are available on births or deaths. It was our impression that the birth rate in the large cities was low—especially among the professional groups. We saw few pregnant women on the streets and few children. Professional people with whom we spoke usually had one child, occasionally two, often none after several years of marriage.

Fig. 3.—Visiting mothers at the Children's Hospital in Moscow.

LIBRARIES

The hospital medical libraries which we visited were very poor. The books are, for the most part, old and poorly printed, and the paper is of inferior quality. The books are not well arranged, space for readers is inadequate, and no effort seems to have been made for the comfort of the reader. We saw few English-language journals. The only English-language pediatric

The reason given for the small number of children was inadequate housing.

RESEARCH

The clinical research which we observed was not impressive. In Moscow a study was in progress on the application of the "conditioned reflex" in the treatment of chorea. On admission the patients were sedated with bromides. Gradually a placebo was substituted

for the bromides until finally the child received only the placebo. The sedative effect continued. With this new treatment, we were told, the length of hospital stay was reduced from ten to six weeks. The statistical criteria would hardly satisfy the critical investigator.

Another study had to do with the effect of aerosols containing various antimicrobials on respiratory infections.

In Leningrad the development of bacterial resistance to various drugs was under study.

In Moscow the reflex responses of infants was being investigated. The babies were completely enclosed in a light- and sound-proof shell, various stimuli were applied, and the responses measured on revolving smoked drums.

PERSONALITY OF THE RUSSIAN CHILD

A striking feature of the Russian child is his docility. We were impressed, in visiting a dental clinic, to see three small children seated in dental chairs accepting the dentists' ministrations without any protest whatsoever. This impression was further borne out by the relatively quiet play of Russian children. When we remarked on the quietness of the children in the hospitals we were told that they had been instructed beforehand to be good.

NURSERIES

Working mothers keep their children in nurseries, many of which are connected with the factories where they work. The children are deposited there in the morning and are generally taken home in the evening. The nurseries which we visited, like the hospitals, were neat and clean and the children seemed contented. We were told by Russians that the nurseries varied widely—some good ones, some bad ones.

We had an impression that putting a child in a day nursery was looked down upon. No person whom we asked—all were of "professional" status—admitted that he himself had been reared in a nursery or that his child was being cared for in a nursery. The replies were that the mother did not work, or that a relative, usually a grandparent, looked after the child while the mother worked.

It is easy to understand how regimentation in a nursery might lead to the docile personality which struck us so forcibly.

On the whole, the doctors impressed us as job-holders rather than professionals. When their short day's work at hospital or clinic is over, they go out and do their shopping—a major task in Russia since there are shortages and consequently much queuing-up, and since the tiny, overcrowded apartments have little space for storing. They then prepare the evening meal. They do not seem to understand the continued interest which physicians elsewhere have in their chosen profession. When told of the long hours spent by American physicians at their work they said it was "not allowed" in Russia.

The principal interest—indeed, perhaps the sole interest of the Russian pediatricians—seems to be in the prophylactic program and in the care of the mildly ill. We saw no evidence of the great amount of time, effort, and money which are spent elsewhere on the care of children who are desperately ill or who have unusual illnesses. At no hospital that we visited did we

happen on a clinical conference. At the large children's hospital in Moscow a conference was held in our honor, but there was no presentation or discussion of patients. Instead, the Director made a flowery welcoming speech and described the prophylactic program. Medicine, like everything else in Russia, seems to be geared to the "greatest good to the greatest number."

We were touched by the warmth and friendliness of the Russian people. Again and again we were accosted on the street by Russians who, in fragmentary English, sought to express their friendliness. At several of the hospitals the young doctors picked flowers and presented them to my wife. At the university a young student undertook to guide us; the "director" of the children's railway in Kiev, a 17-year-old girl, presented my wife with a bottle of perfume; and in Leningrad, a busman, his night's work over and on his way to the garage with his bus, seeing us standing in front of the opera waiting for transportation, invited us into his bus and drove us to the door of our hotel.

Our over-all impression of Russia was one of poverty, drabness, monotony, lack of gaiety. One misses the well-dressed people, fine shops, shiny cars, pretty homes—even garish advertisements. The tree-lined streets and the lovely flower gardens which one sees in abundance in most of Russia's large cities and the occasional imposing public building are not enough to lift the depressing impression.

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Clinical Pathological Conference

THE CHILDREN'S MEDICAL CENTER
BOSTON, MASS.

SIDNEY FARBER, EDITOR
JOHN M. CRAIG, ASSISTANT EDITOR

CLINICAL HISTORIES

CASE 1.—This white male infant was admitted to The Children's Medical Center at 10 hours of age because of cyanosis since birth. He was the product of the third pregnancy of a 20-year-old, healthy mother, whose two previous pregnancies were terminated at full term; both of those children are alive and well. During the eighth month of gestation the mother fell onto the floor and one hour later had the onset of labor, which lasted eight hours and subsided spontaneously. One week later her membranes ruptured and continued to leak small amounts from time to time. She had seven episodes of false labor before going into good labor at term. After eight hours of labor then she delivered, spontaneously, an 8 pound male. There was a great deal of amniotic fluid passed at delivery. Its color was not noted. The placenta was delivered one hour later.

The infant was cyanotic from birth, had abdominal respirations, a pigeon breast, a weak cry, and weak Moro reflex, and was listless. Because of these symptoms, he was transferred to this hospital.

F. H., the father, aged 25, has kidney disease and was a patient in the hospital at the time of birth of the baby.

On admission the infant was weak and cyanotic. The physical examination revealed a temperature of 98° F., a pulse of 148 per minute, and respirations, 48 per minute. The infant's weight was 6 pounds 12 ounces. His length was 51 cm. The chest was bulging anteriorly. The respirations were labored, abdominal in character, and accompanied by subcostal retraction. On auscultation, only faint breath sounds and a few fine râles were heard bilaterally. He responded to painful stimuli with a good Moro response.

The laboratory examination revealed a blood hemoglobin of 22 grams per cent, an erythrocyte count of 4.5 million per cubic millimeter, and a leukocyte count of 10,500 per cubic millimeter. The differential smear contained polymorphonuclear cells, 40 per cent; lymphocytes, 54 per cent; monocytes, 3 per cent; eosinophils, 1 per cent; and basophils, 2 per cent. The lumbar spinal fluid was xanthochromic, with 123 nonerenated erythrocytes per cubic millimeter. The cerebrospinal fluid protein was 386 mg. per cent. The chest roentgenogram revealed a homogeneous opacity

of the right lung with mild, irregular aeration of the left lung. Both lung fields presented a purely granular appearance with no distinct bronchovascular markings.

Course.—The patient was placed in an Isolette, in oxygen and Mistogen, and was given penicillin and streptomycin. For the first twelve hours he seemed to improve, with disappearance of cyanosis, and then the respirations became irregular and slow, as did the heartbeat. The anterior fontanel was not full. He was given, successively, intracardiac Coramine, intratracheal intubation, suction, and positive-pressure oxygen and intracardiac Adrenalin, but respiration and heartbeat ceased at 22 hours of age.

CASE 2.—This white male was admitted to The Children's Medical Center at age 24 hours because of continued respiratory distress from birth. The mother was a 24-year-old, healthy gravida i, para i, whose pregnancy was complicated only by slight vomiting in the first trimester. She had the onset of spontaneous labor one month after her estimated date of confinement, and after seventeen hours of labor without progress or rupture of the membranes was delivered by cesarean section. The cord at delivery was macerated and black; the character of the amniotic fluid is not known. The baby breathed only after seven minutes of resuscitation with oxygen, Coramine, and artificial respiration. After this the color was gray, respirations were rapid, and the cry was high-pitched. At eight, and again at eleven, hours after birth he had two episodes of twitching. The birth weight was 9 pounds.

On admission the infant was very ill, with a gray color, a dry, wrinkled skin and long, meconium-stained fingernails and tongue. The temperature was 100° F. (rectal), pulse 160 per minute, the respirations 56 per minute. The weight was 8 pounds 9 ounces. The pharynx was injected. The chest showed symmetrical anterior bulging with little retraction. The percussion note was dull. There were inspiratory râles in both lungs, more on the right. The lower extremities showed slight edema. There was an active Moro reflex.

The admission laboratory data revealed a blood hemoglobin level of 14 grams per cent. The peripheral leukocyte count was 23,000 per cubic millimeter, with a normal differential count and 15 nucleated erythrocytes per 100 leukocytes. The lumbar cerebrospinal fluid was clear and sterile. A chest roentgenogram revealed an increased anteroposterior diameter of the chest and an enlarged, globular heart. The lungs were hyperaerated but with hazy, irregular densities at the lung bases.

Course.—The baby was given oxygen, mist, a clysis of 60 c.c., Hykinone, penicillin, streptomycin, and Chloromycetin. On the second day he took dextrose and water moderately well, but vomited twice. Respirations continued rapid, the cyanosis increased, and terminally the pulse slowed to 30 per minute before respirations and heart action ceased.

DISCUSSION

DR. FARBER.—The discussion today will consist of a colloquy between Dr.

Murray Pendleton,* a pediatrician, and Dr. Herbert Peterson,** a roentgenologist.

DR. MURRAY PENDLETON.—Both of these babies present, primarily, a problem in the diagnosis of pulmonary disease in the presence of neonatal respiratory distress.

The terms "respiratory distress" and "abnormal breathing" are often used interchangeably; I think these terms should be clarified. The former implies a "labored" component. The latter includes situations in which this is lacking—namely, disturbances of rate and rhythm, such as slowing, marked irregularity of rhythm, and apnea; here a malfunctioning respiratory center alone may be at fault. When "distress" is significant, as in the cases under discussion today, I believe one must consider the presence of some abnormality of the peripheral respiratory apparatus.

When one is attempting to establish a diagnosis of neonatal pulmonary disease under these circumstances, two principal requirements should, in my opinion, be met; the first is mandatory and the second, desirable. First, the diagnosis must be *exclusive*. To be excluded are those conditions outside of the lungs themselves which can cause labored breathing. Whereas such situations are relatively uncommon, their recognition is extremely important, in that they frequently require specific therapeutic measures for survival of the infant concerned. Such primarily extrapulmonary abnormalities are of three types: conditions causing (1) obstruction to the airway (for example, laryngotracheal anomalies or esophageal atresia), (2) compression of otherwise normal lung tissue (diaphragmatic hernia, pneumothorax, unilobar emphysema), and (3) a failing heart (for example, "idiopathic myocarditis," paroxysmal auricular tachycardia, or coarctation). Through the indicated use of diagnostic tools, such as a careful physical examination, the laryngoscope, and the x-ray, these conditions can be diagnosed premortem and often treated effectively by such measures as surgery or digitalization. Second, our diagnosis should be *specific*, if possible, for the particular kind of intrinsic pulmonary disease present. The fact that existing methods of treatment are much the same, regardless of the nature of the process, does not justify our neglecting this step.

In a recent series of 147 newborn infants with respiratory distress and pulmonary disease, studied by Dr. Peterson and myself,[1] there were twenty-seven fatalities. All of these infants' lungs at autopsy showed one of two basic pathologic pictures (mixed in only two cases). These two were hyaline membrane disease and fetal aspiration of keratinized squamous cells and/or meconium. In addition, regardless of the basic process, pneumonia was found in about one-half the lungs, and focal hemorrhage in about one-third. Anectasis, per se, in the absence of an otherwise undamaged respiratory system, was not found and is thought by many, including ourselves, to be rare except in situations of extreme prematurity (twenty-eight weeks' gestation or less).

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Clinically, a consideration of the circumstances surrounding the infant's delivery was more helpful in pinpointing the lung disease than was the physical examination. Maturity, the presence or absence of meconium in the amniotic fluid, the type of delivery, the age at death, and the duration of labor and/or ruptured membranes were most significant. When present, such conditions as maternal diabetes, polyhydramnios, placenta previa, and premature separation of the placenta were thought to contribute.

All the premature infants showed hyaline membranes, and all postmature infants showed fetal aspiration. Mature infants (thirty-eight to forty-one weeks' gestation) had the formation of hyaline membranes about three times as frequently as evidence of massive aspiration of amniotic sac content. All the meconium-stained babies showed fetal amniotic aspiration, in contrast to only one in twenty-three not so stained. Regardless of type of delivery, hyaline membrane formation predominated; however, with pelvic delivery, fetal amniotic aspiration occurred four times as frequently as with cesarean section. As previously mentioned, a mixture of the two processes was occasionally encountered. Infants whose age at death was over 1 day had pneumonia, pathologically, three times more frequently than those who died in the first day (ten of fourteen babies, in contrast to three of thirteen). In the latter instance, prolonged labor and ruptured membranes were present in the case of two of the three babies with pneumonia. This is in accord with the work of Blanc,[2] Hepner[3] and others, who have shown a correlation between prolonged labor or ruptured membranes, chorioamnionitis, and infection, usually pulmonary, in newborn infants. They found no correlation between perinatal events and the occurrence of pulmonary hemorrhage.

The physical examination of the lungs contributed little to the clinical differentiation of these pulmonary disorders. Progressively decreasing resonance, "shortening" of the breath sounds, and fine râles seemed more characteristic of the babies with the formation of hyaline membranes than of those with massive aspiration of amniotic content, where hyperresonance, loud breath sounds, and coarse râles were frequently encountered. Considerable overlap occurred, however, and in neither instance could pneumonia or hemorrhage be eliminated on the basis of physical findings.

With this as background, I will take up the two cases in question today. Both patients had labored breathing and thus, I believe, an abnormality of the peripheral respiratory apparatus, for reasons previously mentioned. That both had pulmonary disease, primary or secondary, seems quite evident on the basis of the physical findings in the lungs.

In case 1, the only positive evidence for an extrapulmonary factor in the peripheral respiratory mechanism is polyhydramnios, which has been found in association with a number of conditions, including esophageal atresia; though this has not been ruled out here, the early onset and the character of the abnormal breathing make it unlikely as a causative factor.

The infant was mature, not meconium-stained, and born by pelvic delivery—all of which give him a much

better chance of having hyaline membranes, rather than particulate aspirate in his lungs; the finding of fine râles and faint breath sounds supports this conclusion. Prolonged rupture of the membranes suggests the possibility of pneumonia in addition.

This baby presented several other features of questionable significance, which I think should be considered as coexistent with, rather than primarily productive of, his respiratory difficulty. A weak cry and listlessness are not necessarily specific for central nervous system damage but merely indicative of severe illness in a general way. However, the findings of xanthochromia and a total protein of 386 mg. per cent in the spinal fluid do suggest intracranial vascular damage. Significant hemorrhage is unlikely in the presence of only 123 erythrocytes at this age; exudation due to infection, old or early, is improbable without pleocytosis. Transudation due to asphyxia, on the other hand, cannot be ruled out. Here, I am inclined to believe the negative Pandy reaction and wonder about the decimal point in the total protein value.

In Case 2, the exclusion of a "peripheral" extrapulmonary factor is not completely justified because of the finding by x-ray of an enlarged globular heart. This could indicate a failing heart due to causes previously mentioned, but I will choose to consider this in the same doubtful category as I did the increased spinal fluid protein in the first case. This does not mean that digitialis should not have been used in this situation, however.

This infant was postmature, meconium-stained, and delivered by cesarean section. The former two factors make the probability of massive fetal aspiration far outweigh that of hyaline membrane formation. On the other hand, the type of delivery suggests that hyaline membranes might be found; a trial of labor preceding section complicates this factor and if this type of disease is present I certainly believe it will be dominated by the picture of massive aspiration of amniotic sac content. Because of the duration of this baby's sickness (greater than forty-eight hours) the probability of superimposed pneumonia exceeds 50 per cent, even without a history of prolonged rupture of the membranes.

Though in my judgment not primarily causative of his state of labored breathing, other features relating to central nervous system damage complicated this infant's course. The combination of passage of meconium in utero, delayed onset of breathing, apparent shock in the first day, high-pitched cry, and twitching seems more significant than in the first case, and probably indicates such damage, presumably by asphyxia. This, rather than his pulmonary disease, may well have been primarily responsible for death and be in evidence at postmortem examination, through the finding of perivascular hemorrhages in the brain and other tissues.

In summary, I believe the first baby will show alveolar hyaline membrane formation, and the second, massive fetal aspiration of amniotic sac content, pneumonia, and evidences of asphyxial brain damage. As must be evident by now there has been a lot of guesswork involved, and both cases show clearly the need for some tests which would enable the clinician to

be more exact and certain in his diagnosis of pulmonary disease. Dr. Peterson may be able to help us here.

DR. FARBER.—Thank you, Dr. Pendleton. Dr. Peterson.

DR. HERBERT PETERSON.—I think the best way for me to try to place these infants in their proper categories is to refer again to the accumulated experience which we have had at the Boston Lying-in Hospital with 147 newborn infants who have had the onset of respiratory distress in the immediate neonatal period. That is, this was evident either at birth or within a very few hours after birth. Of these 147 patients with respiratory distress secondary to intrinsic pulmonary disease, we have had 138 who seemed to us to present one of two quite different and quite distinct patterns by x-ray. The most common, which was evident in 104 of these babies with disturbance of x-ray patterns, is characterized by a diffuse, fine, miliary, granular, or stippled increase in density throughout both lung fields, which may not be entirely uniform in all layers. Another feature of this pattern is the outlining of the air-filled tracheobronchial tree abnormally far into the peripheral lung fields. In spite of the fact that these lungs present a generally increased density, they appear to be well expanded as judged by the position of the ribs and the domes of diaphragm. The ribs, thus, have the normal horizontal infantile position, and the domes of diaphragm are quite well down. The patients who have presented this coalescent, homogenous, finely granular density, either throughout both lungs or in a major portion of the lungs, have shown alveolar hyaline membrane formation at autopsy. Yet, with this homogenous or coalescent density, it has been difficult (from the x-rays alone) to exclude the presence of other pathology, such as pneumonia, intrapulmonary hemorrhage, or some aspiration.

A totally different and quite distinct type of pattern, seen in thirty-four out of the same 138 infants, was a coarse thickening and irregularity of the interstitial markings, fanning out into the lung fields, in contrast to the previous group, with areas of emphysema, of consolidation or atelectasis, and of normal aeration. In addition to this irregular pattern of increased density, there was a hyperexpanded state of the chest, giving a crablike appearance, with a low, flattened diaphragm and a bulging of the anterior chest wall. At 1, or 2, or 3 hours of age these infants, from the chest films, looked as if they could survive only a very short period of time. Sometimes within twelve hours, and usually within twenty-four hours, they have a remarkable clearing of the lung fields. If you were to see a film from such an infant at 48, or even at 24 hours of age, as a single examination, without knowledge of what had been going on previously, it would be difficult to guess its previous appearance. I think that such patterns, very likely, have been interpreted on the basis of twenty-four- and forty-eight-hour films as a bronchopneumonia or a congenital pneumonia—yet it is a process which clears too rapidly to be a true inflammatory or infectious one. These, we believe, represent gross aspiration of amniotic sac content.

Previous experience has led us to regard prematurity and delivery by

cesarean section as the two most frequent clinical features associated with the finding, pathologically, of alveolar hyaline membrane. In contrast to this, the "fetal aspiration syndrome" has been associated with postmaturity and meconium staining. In such fatal cases, larger amounts of keratinized squames, meconium, or both, are found in the bronchioles and alveoli. The lungs usually display emphysema and a segmental or irregular aeration of the lungs.

Now, in correlating the two patterns with these two clinical and pathological states, the majority of babies, we find, with the reticulogranular "hyaline membrane" pattern (90 per cent of them, or 95 of 104 in actual number) were either premature, or delivered by cesarean section, or both. All of those who died in their initial illness had hyaline membranes, generally distributed throughout the lungs. In contrast to that, we find that of those presenting the coarse, irregular "aspiration" pattern by x-ray, 85 per cent were either postmature or had meconium staining of the skin, or both. All four of this group who came to autopsy showed large amounts of aspirated keratinized squames or meconium in their distal bronchi. All of them showed irregular aeration of their lungs, with emphysema.

In the first patient (Figs. 1 and 2) there is a uniform increase in density throughout the entire right lung, with an area of density in the left upper field, a little better aeration in the left apex, and perhaps a little better aeration at the left base. The pattern is fairly uniform throughout both lungs, characterized by an increase in density, and on inspection of the films one can make out a faint granularity in the pattern, particularly through the upper portion of the stomach air bubble. In addition to this fairly uniformly increased density with a faint granularity to it, there is the outlining of the air-filled tracheobronchial tree far out into the lung. This can be seen only if the adjacent parenchyma is either atelectatic or filled with some solid material having a soft-tissue density. There is not any particular irregularity of aeration here though there is some difference of aeration. I would place this in the predominantly hyaline membrane formation picture because of the coalescence and the lack of definition of the parenchymal process. I would not be able to exclude the presence of pneumonia or even of hemorrhage.

The film on the second infant presents quite a different appearance (Fig. 3). The domes of diaphragm go rather sharply and obliquely downward. The lungs in general are hyperaerated. There is some focal irregularity of aeration. There are two small patches of density at both bases. The heart has a globular appearance and it is enlarged. On a lateral view, there are the additional changes suggestive of either a pneumomediastinum or a herniated lung. I would like to emphasize that the films on this baby were taken two days after his admission here, when he was 72 hours old. In other words, we are looking at the films of an old man, compared to the time of his birth. I would consider the roentgen pictures to be compatible with a clearing aspiration pneumonia on the basis of some of the focal irregularities. I cannot say what abnormality is underlying the small basilar densities, but I would like to

Fig. 1.

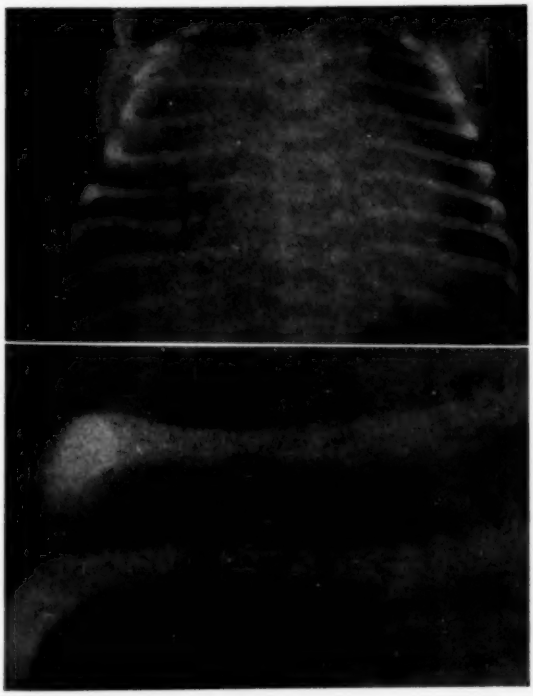

Fig. 2.

Fig. 1.—Roentgenogram of chest. There is a homogeneous opacity of the right lung. Case 1.

Fig. 2.—An enlargement of right lung field to show the granular pattern of the lung. Case 1.

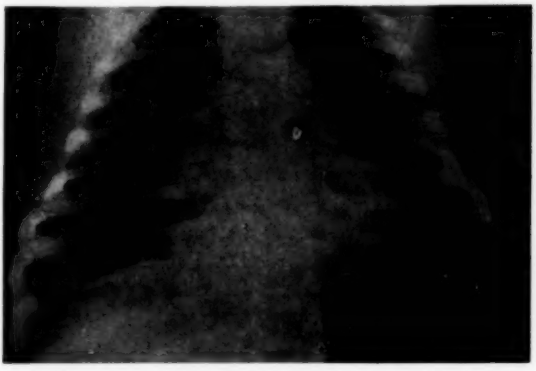

Fig. 3.—Roentgenogram of chest. The lung fields are hyperaerated; there are irregular densities at the lung bases. Case 2.

say that from the standpoint of the lungs alone at this particular time, I would suspect that there was some other cause contributing to death.

DR. FARBER.—Thank you, Dr. Peterson.

I think we will ask Dr. Craig to present the findings now, and then I hope we will have some comments from Dr. Clement Smith. Dr. Craig.

DR. CRAIG.—Well, I had hoped to confuse Dr. Pendleton and Dr. Peterson, but I am afraid I did not do it. The fact that the first child weighed 8 pounds when he came here, and the fact that in the second child the lungs were described as clear or hyperventilated, I had hoped, would throw them off the scent. It is going to be evident that both gambits failed.

In the first case, the lungs were collapsed and airless. They were considerably overweight—35/24 grams for one and 28/22 grams for the other. The lungs were soft, flabby, bright pink in the anterior and dark purple in the posterior lobes. They were, just as Dr. Pendleton predicted, beautiful examples of hyaline membrane formation with numerous broad hyaline membranes lining the alveolar ducts and appearing in the alveoli, which were markedly congested. Many areas had numerous contiguous, unexpanded alveoli. In the hyaline membranes nonkeratinized, as well as many keratinized, squamous cells were included. There is great debate among pathologists as to the origin of these structures. Whether they are formed from exudate or from transudate, as we believe,[4] or in part from material aspirated from the amniotic sac is still to be determined. I have been particularly interested in the fact that unlike most of the hyaline membranes that are formed from other kinds of chemical or reactive processes, such as you get in rheumatic pneumonia or after influenza, these show rather a more particulate character. (Fig. 4.)

In the second child, the lungs were moderately collapsed, airless, and quite firm. They were dark purple in color but they filled about 75 per cent of the pleural cavities. The alveolar ducts, the terminal bronchioles, and often many adjacent alveolar spaces, were completely plugged with masses of squamous cells. This was true of most areas of the lungs (Fig. 5). One upper lobe had a somewhat different finding. In this area one can see a transition between the picture of massive aspiration of squamous material and a recognizable hyaline membrane. In a few areas there were quite well-formed hyaline membranes. There was very little inflammation in this lung. I think that our pathological findings correlated well with Dr. Pendleton's clinical and Dr. Peterson's radiological interpretations, which predicted that the first infant would have, predominantly, a picture of hyaline membrane formation, congestion, and atelectasis, and that the second infant would show evidence of massive aspiration of amniotic sac content in alveoli.

There are a few things which bothered me about Dr. Pendleton and Dr. Peterson's ideas. If we take Dr. Landing's data,[5] which showed that as term approached there was a gradual increase in the number of squamous cells in the amniotic fluid, why do we not have a smoother transition between the two states, with many more mixed

Fig. 4.

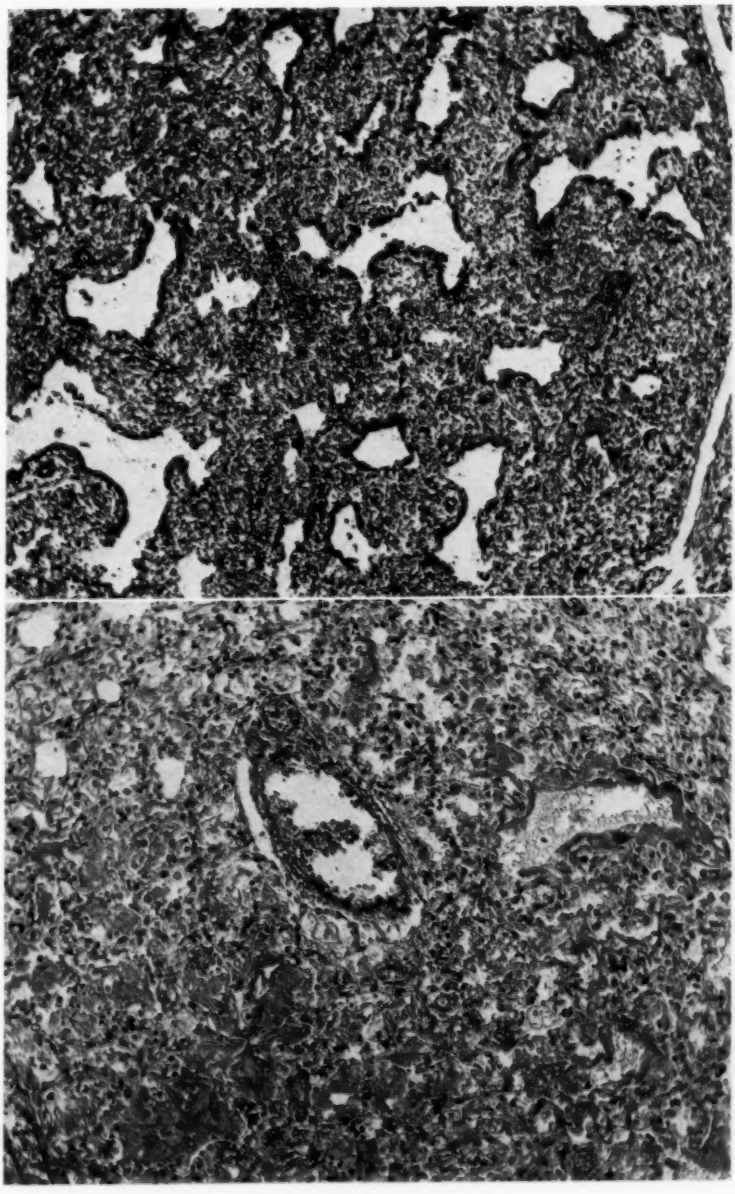

Fig. 5.

Fig. 4.—Photomicrograph, lung. Atelectases, emphysema of alveolar ducts, hyaline membrane formation, and congestion are present. Case 1. (Hematoxylin and eosin; ×125; reduced ⅛.)

Fig. 5.—Photomicrograph, lung. The alveoli are expanded but filled with aspirated amniotic debris. One hyaline membrane is seen. Case 2. (Hematoxylin and eosin; ×180; reduced ⅛.)

pictures than they have been able to demonstrate?

The second feature that is interesting with fetal aspiration is why a lung of a child clears so rapidly. We see that, pathologically, the lung alveoli are plugged with these squamous cells, and it is difficult to believe that these will clear within such a short period of time. The aspirated squamous cells in older children seem to be much further down the respiratory tree than in the case of the hyaline membranes in the younger children, which seem principally to be in the alveolar ducts and atria.

DR. FARBER.—I think the explanation of the clearing may lie in the fact that, when first aspirated, the amniotic sac material may lie in the bronchioles, partially or completely blocking them, giving alternate areas of atelectasis and obstructive emphysema. As respiratory efforts continue, this material may be drawn further down the respiratory tree into the alveolar spaces, and thus give an appearance by x-ray of clearing. Dr. James L. Wilson and I thought we could mimic that quite well many years ago, experimentally.

DR. CLEMENT SMITH.—The material that Dr. Peterson and Dr. Pendleton have shown us has been very helpful. I think it has been more helpful with regard to the second entity than to the first. You can understand what happens in the presence of a meconium-stained amniotic fluid in the lung, and expect just such a picture as they describe. In the first baby, the difficulty lies in the importance of the hyaline material seen pathologically, in the etiological or physiological pathology of the whole process. It is still unfortunate that that particular entity in a situation marked by a considerable degree of congestion and other factors has been selected as the name of the syndrome. Dr. Wilson, in a recent discussion, pointed this out very nicely. I hope Dr. Craig may have the opportunity of telling us, sometime in the future, whether he feels that the cause of death from hyaline membrane is sufficiently clear to justify this terminology. It is hard to know why these premature infants should have this degree of material in their lungs. From the studies of Dr. Blystad and associates[5] one would have to presuppose that there was a tremendous amount of amniotic fluid. I tend to discard the amniotic fluid as the source of the hyaline material and wonder whether the ultimate explanation of the hyaline material will not be pulmonary capillary transudation of protein, or something involving circulation fully as much as aspiration. The suggestion recently made, more or less as a matter of speculation, in the *New England Journal of Medicine*[6] that oxygen poisons these babies and may be a cause of hyaline membrane formation, has I think, been properly touched on by Dr. Craig, in that not only are these membranes rather different in appearance from those that can be produced by the administration of oxygen in animals, but also it appears to be harder to produce such effects in the lungs of very immature animals. The fact that the longer one has the chance to give oxygen the better chance of survival these babies have would stand in my mind against the implication of oxygen in the production of the membranes.

DR. FARBER.—I think there is no question that, if one takes experimen-

tal animals and subjects them to an atmosphere of 95 or 100 per cent oxygen, there is injury to the vascular system in the lungs and an outpouring of protein-rich material, which is forced against the alveolar duct and alveolar walls. That is not the picture which we have seen here in these infants. I think one gets into difficulty with the so-called "hyaline membrane disease" only if one assumes that in all cases the appearance is caused by exactly the same material or the same mechanisms. If one does not make that assumption (which I believe is a false one), then there is not quite the same problem. I believe that this is a mechanical situation which may be produced by a number of different agents in a number of different ways. The composition of this material varies according to its source. I think that we can identify vernix. I think we can differentiate that from protein-rich serum which may be forced against alveolar walls. We must not forget that when we get the first vernix membranes, we have then a cause for the outpouring of protein-rich serum as a complication when asphyxia occurs. I want to emphasize what Dr. Craig brought out—that these keratinized epithelial cells are not confined to the postmature infant at all; they are present in large numbers in the eighth and ninth months, particularly in the last month of pregnancy, and the fluid in the amniotic sac varies greatly in its content. Dr. Smith and Dr. Landing, in their studies, documented by careful cell counts what had been recognized for a long time. Keratinized epithelium may dominate the picture in the last month of pregnancy, or at birth. The reasons that they are not present in large numbers in premature babies' lungs is explained by the well-known fact that squames do not begin to peel off until the latter part of pregnancy.

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Medical Progress

PROGRESS IN NEUROPSYCHIATRY

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RECENT advances in psychiatry have been substantial and exciting, if somewhat less spectacular than Madison Avenue's claims on their behalf. Comparative studies in child-rearing practices and in early learning are clarifying the impact of culture on personality and intelligence. The renaissance of interest in hallucinogens and ataractics promises not a tranquilized future but real gains in our knowledge of neuropharmacology. The function of discrete brain areas is being systematically explored with implanted microelectrodes and operant conditioning. Biochemical investigations are identifying specific enzymatic defects associated with central nervous system malfunction. Epidemiologic methods are being applied to the search for the statistical correlates of disturbed behavior. The mind-body dualism that has plagued medical psychology has by no means been resolved, but we are beginning to perceive, if only dimly, the interrelations between the physiologic, the psychologic, and the social levels of integration.[1-4a]

As certain of the newer concepts in neuropsychiatry have not as yet appeared in the pediatric literature, it seemed appropriate to review them briefly. Topics of interest to the reviewer and, in his estimation, relevant to pediatrics have been selected for discussion; for more complete accounts of the clinical and experimental literature, the reader must be referred elsewhere.[5-8] If this review succeeds in stimulating its readers to turn to the references cited, it will have accomplished its major purpose.

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GENDER ROLE AND PSYCHOSEXUAL ORIENTATION

Few characteristics of personality are so deeply imbedded, so permanent a part of the matrix of behavior, as sexual role and orientation. By posture, body movement, inflection and mode of speech, choice of language, and values, the very great majority of the members of any society can be identified as male or female, without regard to the superficial signs of identification by grooming and dress. With the significant exception of the psychosexual deviants, maleness (as defined by the culture) and male body structure and femaleness (so defined) and female body structure are so universally associated one with another that the characteristic personality type has been assumed to be a simple consequence of the structural

and biochemical specificities of each sex. Yet a nagging doubt has always existed because of the notable exception of the invert. Myriad investigations of the hormonal output and the body physiology of the psychosexual deviant have failed to reveal the anticipated disorders in chemical and structural economy. Indeed, recent studies of sex chromatin patterns as indicators of genetic sex in homosexuals have revealed each to be typically the sex of physical and not psychological type.[9, 10]

It has long been known that lower animals can exhibit both male and female patterns of sex behavior, subject of course to the limitations of physical structure.[11] True, in certain of these organisms (most notably, birds), one or the other pattern can be selectively induced by administration of the proper sex hormone. As the evolutionary scale is ascended, however, the dependence of sex behavior on hormonal influences becomes far less complete. In the cat, for example, experience prior to castration may be decisive in determining subsequent sex patterns.[12] In the chimpanzee reared in captivity, the assumption of a mature sexual role is possible only if heterosexual exposure has been provided at a sufficiently early age.[13] Even an experienced sex partner may be unable to evoke the proper responses in a previously deprived mature animal.

By extrapolation, we should anticipate that postnatal influences will be even more decisive in man, whose specifically human characteristics are a product of social interaction mediated by an enormously developed forebrain. But perhaps few would have dared predict that sexual orientation would prove to be almost exclusively determined by mode of rearing. Yet this seems clearly the case on the basis of the remarkable studies carried out by John Money and John and Joan Hampson.[14-20] These investigators took advantage of the unparalleled opportunity provided by Wilkins'[21] clinical cases of pseudo and true hermaphroditism. Here were the experiments of nature: individuals in whom chromosomal, gonadal, hormonal, external genital, and secondary morphologic sex were discordant in various combinations. The ambiguity of genital morphology had often resulted in an assignment of sex to the individual which contradicted the sex chromatin or gonadal sex, the discrepancy to be discovered incidentally at a later age or as result of the failure to progress congruently in adolescence. These patients were studied thoroughly by psychologic and psychiatric methods and their psychosexual patterns compared with their physiologic characteristics.

The striking result of these studies is the discovery that psychosexual orientation correlated with assigned sex of rearing and not with chromosomal, hormonal, gonadal, or genital sex. A gender role fully concordant with that of rearing was established by nineteen of nineteen patients with a contradictory sex chromatin pattern, seventeen of twenty with a contradictory gonadal sex, twenty-three of twenty-seven with a contradictory hormonal sex, and twenty-two of twenty-three with a contradictory external genital morphology.[14] For example, patients with a male sex chromatin pattern and testes (albeit estrogen-producing testes) were feminine in gender role and orientation, since they had been raised as girls;

patients with a female sex chromatin pattern and ovaries, whether hormones were male or female, proved to be masculine in gender role and orientation, since they had been raised as boys. The parents of these children had regarded them as normal girls or boys and had treated them accordingly. The children responded by establishing a pattern of psychosexual behavior that conformed with the demands of their culture.

Even those cases with ambiguity in external genital morphology established thoroughgoing and culturally conforming gender roles, so long as no doubt as to handling, no whispered uncertainty existed in their families. These patients were concerned with their anatomic problems, but much as an arthritic is disturbed by his orthopedic handicaps; they did not doubt their basic sexual identity. The girls with virilizing adrenal tumors wanted and welcomed medical help to overcome the unsightly hair, the failure of menstruation, etc., but they did not for a moment question that they were girls or fail to behave in a feminine fashion. With few exceptions, when medical help was sought, it was sought to preserve sex of rearing, though this might prove considerably more difficult and physically less satisfactory from the surgical standpoint. Psychologic unhealthiness, when it existed, was found in the cases in which rearing patterns had been changed by parents on ill-advised medical opinion or in which the family attitude was governed by secret fears that the children were not "real" boys or girls but "morphodites."

Indeed, these studies have important semantic and therapeutic implications for the very definition of sex. Each of the indices of sex—chromosomes, gonads, hormones, genitalia, gender role—can vary discordantly with one or more of the others. Which one, or which combination, shall be decisive in determining sex? In the first year of life, the decision must be based upon diagnosis of the clinical syndrome, knowledge of its probable course of development, the functional results of plastic surgery, and the utility of hormone therapy. The aim will be to assign to the patient that sex role which he will be able to fulfill most physiologically after appropriate therapeutic modification of his native anatomic equipment. But, once a decision has been taken, whether wise or foolish, and the child reared accordingly, the imperative consideration in medical management is his own conception of his gender role. The patient with a male sex chromatin pattern and testes but a feminine psychosexual orientation should be regarded as a *girl* (without quotation marks), albeit an infertile one, from the standpoint of her function in society as a person.

The external genitalia of the newborn infant serve as signs to family —and later to the child himself—that this child is a boy or girl. From then on, the expectations of the culture ensure the appearance of what that culture considers appropriately masculine or feminine behavior. The child is surrounded by elaborate systems of reward and punishment, direct and subtle pressures, all designed to guide his development along culturally determined channels. Obviously, biologic maturation adds the final touches, timbre of voice, hair, body configuration, genital conformation, that solidify the identification and facilitate physiologic function. But the basic

pattern has already been set—beyond the possibility of modification without severe intrapsychic repercussions—before puberty.

This conception of the development of psychosexual role and orientation as a result of life experiences encountered and transacted suggests that the genesis of deviant psychosexual patterns is to be sought in atypical, nonnormative life experiences. Careful clinical study of psychosexually deviant children tends to validate this expectation. In most cases, we can trace the roots of deviant sex behavior to such factors as the unacceptability of the patient's anatomic sex to one or both of his parents, premature seduction into genital activity, lack of adequate models for identification, and so on. The elucidation of causes does not, unfortunately, always imply the possibility of alteration of the behavior. When we recognize how firmly normal patterns are set, we must be prepared to acknowledge that pathologic patterns may be no more easily modified. The shift in our conception of etiology from hormones to psychic influences should not be confused with a transition to a necessarily simpler therapeutic task.

Indeed, the development of gender role provides an illustration of an induced pattern of behavior, so imbedded in the personality and so pervasive in its influence, that heretofore it has been regarded as determined in an automatic, mechanical, or instinctive fashion. Yet, on close study, we can only conclude that its source lies in the psychosocial environment. Need it be argued any longer that psychic influences are real, durable, and potent?

EARLY EXPERIENCE AND SUBSEQUENT BEHAVIOR

The relative influence of innate versus acquired elements in governing behavior has long been the subject of acrimonious debate. Innumerable studies have been undertaken in the vain hope of determining whether a given bit of behavior is inherited *or* learned. Asked in this form, the question is unanswerable. To "prove" that the behavior under study is not learned requires that all possibility of relevant learning be excluded; but to do so is not possible until the precise mechanism and ontogeny of the behavior pattern is fully understood. The prior experience necessary to the complete act is often far more subtle than the naive experimenter may suppose. True, a rat at parturition will make nests even if she has never seen any made,[22] but she will not do so when materials are provided if she has been previously denied the opportunity to manipulate straw, food pellets, etc.[23] Again, one may observe "maternal behavior" in a rat reared in isolation prior to fertilization. Apparently, then, this is "instinctive." Yet, if the rat, in addition to isolation from others, be prevented from smelling or licking her own body, she will devour rather than mother her offspring.[24] In both instances, earlier part-processes have had to be incorporated in the behavioral repertoire through experience before the complete act could make its appearance in response to central maturation. Moreover, even the most exclusive process of genetic development in any living organism is dependent upon environmental interaction, at the least for energy supply, essential metabolites, etc., and is in this sense

environmentally determined. Contrariwise, the most propitious environmental circumstances avail naught if the genetic capabilities for developing and accommodating in response to those circumstances are not present within the fertilized ovum.

Surely, we must begin with the recognition that any behavior exhibited by an organism is a consequence of a genetically elaborated central nervous system modified by previous life experience. *All* behavior is *both* learned *and* acquired.[25] To ask whether it is one or the other is to ask whether the area of a field is due to its length or its width. The only meaningful question we can ask is: with heredity (or environment) held as constant as we can, how much variance in the item under study can be induced by varying environment (or heredity)? At the same time, we must choose conditions of environment and heredity that will permit variation to occur.[26] We would hardly propose to examine the effect of culture on intelligence test performance by comparing microcephalics reared in stimulus-poor and stimulus-rich environments; the inherent structural limitations would override experiential factors. Similarly, we would be ill-advised to investigate hereditary influences on intelligence by studying the verbal I.Q. of children brought up in an illiterate society; the cultural poverty would mask potential intellectual variations.

Genetic factors limit the permissible behavioral repertoire of the organism. The chimpanzee, reared in a human household with tender solicitude, becomes nothing more than a chimpanzee, if a somewhat aberrant one.[27] But the restriction set by inherent central potentialities acts over a rather wide range; within that range, experiential factors may have a profound influence on the actual levels of performance achieved. Recent evidence from animal and human studies has tended to emphasize the pervasive influence of early life experience on subsequent behavior. Even microorganisms can be permanently modified in metabolic behavior by environmental agencies: the addition of transforming substance to pneumococci[28] or penicillin to colon bacilli[29] will induce persisting changes. The "instinctive" return of the adult sawfly to oviposit on the species of willow tree on which it fed as a larva can be altered for subsequent generations by the expedient of transplanting the eggs to an unpreferred species which now exerts the same compelling attraction.[30]

To turn to examples more germane to our clinical interests, we find that rats reared in a stimulus-poor early environment are deficient in "intelligence" (maze-solving ability) as compared with their normally reared littermates.[31] The puppy which is reared as an isolate in a bare cage will grow into a dog who differs significantly in "emotionality" and laboratory "intelligence" from his normally treated sibling.[32] Behavior traits, such as aggressiveness and hoarding, have been modified by manipulation of early life experience.[33, 34] In general, these environmental influences are far more potent early in life than later.[35]

The ethologists,[36, 37] who study animal behavior in natural habitats, have advanced the interesting observation that, for certain species (mostly birds), there are brief critical periods for a special type of "permanent" learning known as imprinting (Prägung) (but

compare Lehrman's illuminating critique[38]). The graylag goose, for example, if exposed to a human being immediately upon hatching, will follow that person preferentially and ignore adult geese to do so.[37] Lorenz has filmed the amusing behavior of goslings following him about in the farmyard and even pursuing him in flight while he cycles about the countryside. Other studies have shown that acoustic signals and moving boxes serve as adequate stimuli to induce following behavior in particular species, if exposure occurs during the first few postnatal hours.[39] Such experiments, if one ignores the many negative examples, provide tempting models for the permanence of early childhood memories. Extrapolation is not warranted, however, since imprinting phenomena have been demonstrated in relatively few species and have not been confirmed as such in man.

The following behavior of the gosling, though normally evoked by its "mother," is, after all, a stereotyped biologic response to a pattern of visual and auditory stimuli presented during a critical early period; it is not to be confused with the human response to the symbolically and culturally elaborated concept of mother, whose early biologic matrix is only one determinant of its course. It is all too easy to read into animal behavior anthropomorphic conceptions and then to draw false analogies from nonhomologous and qualitatively different spheres of function. Nonetheless, the observations themselves are highly interesting and deserve further exploration.

This brief excursion into the extensive psychologic literature[39] on early learning provides a framework in which to view the significance of lack of mothering for human infants. Pediatricians have long been aware of the behavior syndrome frequently (though not always) exhibited by infants reared in institutions.[40, 40a] This clinical syndrome, termed hospitalism, includes poor growth on a calorically adequate diet, susceptibility to febrile episodes and infections, apathetic behavior, and lag in developmental indices. The reports of Spitz[41-44] have been regarded as providing a statistical underpinning for these clinical facts. Unfortunately, as pointed out in a recent sharply critical review,[45] close examination of Spitz's data raises many questions as to the adequacy of his studies, questions which have not been satisfactorily answered.[46, 47] Yet the reports of clinicians in many countries concur so remarkably in substantiation of the concept of maternal deprivation that it would seem to be warranted to regard it as clinically valid.[48-48b]

The human organism, so remarkably plastic in its adaptational capacity and so dependent upon social interaction for its specifically human qualities, requires from birth onward a close interrelationship with mothering adults. The institutionalized infant, provided only the minimum of human contact necessary to maintain physical survival and unable to form a relationship with an identifiable other person because of shifts of personnel, has a deficit in the vocal and visual stimuli that normally elicit mimicry, the key to the early socialization process. His tentative efforts to reach out to the environment are not rewarded, as in the mothered infant, and tend to diminish, if not atrophy altogether. He exhibits both intellectual and social deficiencies

in responsiveness. Telling in this respect are the studies of Goldfarb.[49, 50] Children, reared for the first three years of life in an emotionally sterile but physically adequate institution and then placed in foster homes, were found to display lower measurable intelligence and emotionally flat antisocial behavior when contrasted with children reared in comparable foster homes from infancy.[51]

It does not appear that social maturation is dependent upon mothering in the narrow sense of an intense relationship between the child and his own mother. The experience of collectively reared children in Israel indicates that a child-centered culture conveyed through special nursery workers, despite the attenuation of the traditional Western family structure, can supply the emotional nurture necessary for adequate growth and development.[52] These children, reared in children's houses until adulthood, though with maintenance of regular contact with their biologic families, have apparently grown into socially adequate members of their society. In passing, it might be noted that homosexuality is said to be unknown among the adolescents and adults of this group.[53] This child-rearing practice, born of necessity during the pioneer and war years of a struggling nation among a dedicated and intellectually sophisticated population, is being gradually abandoned, a fact which may indicate that it fails to meet important human needs; nevertheless, it has provided a striking indication of the range of social structures within which human growth is possible.

Many claims have been made for the specificity of behavioral consequences produced by maternal deprivation. Early, it is said to result in "anaclitic depression,"[43] late in "affectionless" psychopathy.[54] Evidence to the contrary is provided by other students of the subject.[55, 56] The fact, however, that some children may be able to survive the consequences of maternal deprivation hardly argues its unimportance any more than the fact that not all children get acute nephritis minimizes the significance of streptococcal infections. Those children who have been scarred are so refractory to conventional treatment that the only effective measures presently available are in the area of prevention.[48]

If illness or death of a parent or abandonment of a child necessitates placement, the home provided should ensure not only physical sustenance, but psychologic nurture as well. Foster homes are obviously preferable (if well selected) but institutions can and should be humanized by increasing the ratio of personnel, by grouping the children in small units assigned to particular nursery workers, and by constantly evaluating the extent to which institutional routine meets the requirements of family living.

In hospital care, these principles have equal validity. Our medical responsibility does not end with physical and laboratory diagnosis and the institution of specific chemical therapy. The traditional medical and nursing attitude of regarding visits from relatives as a barely tolerable misfortune for staff and patients must be radically altered. Parental visits (in most cases, at least) are an important part of therapy. With recognition of their essential contribution to the child and with the exercise of some ingenuity, parents can be worked into the hospital program as aides to the nursing personnel.[57, 58] The hazards of cross-infection have been emphasized out of

proportion to the hazard of psychologic isolation for the child hospitalized for any considerable period. Pediatric rounds should be conducted with sensitivity to the child as a sentient being. Only if the physician, as the leader of the hospital organization, recognizes the importance of the psychologic state of the child can he succeed in overcoming the passive opposition of the "efficient" nurse or house physician who sees play activities and prolonged visiting hours as barriers to the orderly function of the ward.

PHRENOTROPIC AGENTS

Knowledge that the ingestion of certain natural substances could result in altered mental states can be said to predate the invention of written language. Preliterate peoples in all sections of the globe employ the euphoric or hallucinogenic properties of fermented sugars and plant extracts in magic and religious rituals. In the Greek era, the theory of humors, espoused by the Hippocratic school, implied the determination of personality traits by chemical actions on brain, the organ of the mind. Since the development of psychiatry as a medical specialty, theories have been prevalent that toxic substances might underlie psychotic states. The postulated metabolic derangements have varied with the changing medical fashions of each era. As successive hypotheses failed to be verified experimentally, biochemical studies were limited to the efforts of the dedicated few.

Within the past decade, however, a tremendous impetus to neurochemistry has been provided by two parallel developments. The first was the accidental finding[59] that lysergic acid diethylamide (LSD), administered in vanishingly small dosage,[60] can induce psychosis-like states in man.[61] The second series of discoveries began with the clinical observations that Rauwolfia derivatives, employed for the treatment of hypertension,[62] and phenothiazines, developed as antihistaminics,[63] possessed the equally remarkable property of ameliorating psychologic dysfunction. It is for both classes of drugs, "psychotomimetic" and "ataractic," that the generic term "phrenotropic" has been proposed to designate their common property of influencing the mental state with relatively little clouding of consciousness and few of the "organic" signs that previously known agents exhibit.[64]

The literature on phrenotropic agents is far too extensive to permit summarization in this brief essay; moreover, their clinical aspects are by now familiar to every physician within reach of mail service or detail men. Indeed, the employment of ataractics in medical practice has reached astonishing,[65] even alarming,[66, 66a] proportions in the four years they have been commercially available. Yet the difficulties of clinical evaluation of psychiatric illness leave many questions incompletely answered as to their true effectiveness and possible "behavioral toxicity." Physicians who have had to cope with the enormous human problems in large state hospitals have, in general, been far more positive as to the value of tranquilizers than have those working in the more favorable circumstances of university psychiatric pavilions. All, however, would appear agreed at this point that chlorpromazine and reserpine play a useful role in the management of the acutely disturbed patient; what their contribution may be to the resolution or likelihood of recurrence of the psychosis is

yet to be determined. In pediatric psychiatry, it is less certain, but still probable, that they are valuable in the management of the hyperkinetic child, whether he be psychotic,[67, 68] defective,[69, 70] brain-injured,[67] or a behavior problem.[68, 71]

But perhaps the most lasting service provided by the enthusiasm for these agents will prove to be the stimulation of research in basic neurochemistry and neurophysiology, as these may be related to states of altered mental function. A number of theories have been proposed,[72] all of which, as currently formulated, are likely to be inadequate but remain important nonetheless as stimulators of investigative curiosity.

The experimental finding that LSD antagonizes the peripheral action of serotonin (5-hydroxytryptamine),[73] a neurohumor present in brain,[74] led Wooley and Shaw[75] to propose that disturbances in serotonin metabolism might be the common denominator in psychoses. Further impetus was provided by the discovery that reserpine causes the release of "bound" serotonin from depots in brain.[76] Serotonin itself produces marked peripheral effects when given intravenously and, further, fails to cross the blood-brain barrier.[77] However, its precursor, 5-hydroxytryptophan, converted by brain decarboxylase to serotonin,[78] will pass the barrier and has been shown to reverse, at least temporarily, the EEG changes in liver coma.[79] Wooley and Shaw[77] have synthesized a benzyl analog (BAS) which functions as an antimetabolite of serotonin. They have embarked on a clinical investigation of the action of BAS and 5-hydroxytryptophan, and others[80, 81] of the action of BAS alone, on the clinical behavior of psychotic patients.

Attractive as are the facts marshaled above, there are others which do not fit the hypothesis that serotonin is the mediator. Brodie and collaborators have demonstrated that reserpine releases not only serotonin but also norepinephrine from the brain.[82] Moreover, chlorpromazine, benactyzine, and meprobamate, all tranquilizers, do not cause serotonin release.[83] Most inconvenient for the hypothesis is the finding by Cerletti and Rothlin[84] that d-2-brom-LSD will antagonize serotonin peripherally, but does not produce the central effects of LSD; this makes it difficult to establish a simple correlation between the "model psychosis" produced by LSD and its antiserotonin properties.[85, 86]

A second chemical hypothesis centers about epinephrine and its possible abnormal metabolites.[87] There are tempting structure similarities between epinephrine and mescaline, an hallucinogen, and between adrenochrome (an in vitro oxidation product of epinephrine) and serotonin, both indoles. Adrenochrome[87] and adrenolutin[88] have been described to be psychotomimetic in man, though some dispute exists.[89] As yet, neither has been isolated in patients. Current investigations should provide data that will discriminate between these formulations and suggest still others.

At the same time, neurophysiologists have been exploring the effects of phrenotropic agents on neural function. Attempts have been made to correlate observed alterations in the electroencephalogram of experimental animals with known properties of the reticular arousing mechanism.[90-92] Suggestive as such attempts are, they suffer from the inherent limitation that the EEG is an algebraic sum of the

electrical action of a complicated neural network; reading from effects to causes is quite speculative. One need only consider that the change produced by stimulation of inhibitory centers may not be differentiable from that produced by direct suppression of excitatory centers; yet the underlying mechanism is quite different in the two instances.

More profitable are more discrete analyses of known projection systems. Marazzi and co-workers[93, 94] have utilized the transcallosal projection system from one visual cortex to the opposite hemisphere in cats. They have shown that LSD, serotonin, and mescaline inhibit the postsynaptic component of this response. Purpura,[95] studying LSD effects on evoked cortical auditory and visual responses, found facilitation of the primary response to click and light, respectively, and alteration of the recovery cycles. His detailed investigations suggested that LSD inhibits axodendritic transmission while facilitating axosomatic, at least in the systems studied. These few citations will serve as examples of an extensive literature, recently reviewed by Evarts.[96]

The neurophysiologic data available to the present, no less than the neurochemical, do not permit a point-to-point correlation with psychologic effects. They remain significant nonetheless as harbingers of an era of productive research which is as important for basic as it is for clinical knowledge. One does not have to choose between a chemical and a psychologic hypothesis as to the etiology of psychosis. It is as readily conceivable that prolonged psychologic stress, acting perhaps through the hypothalamic-pituitary-adrenal axis, could induce persisting chemical pathology as it is that a virus, a genetic defect, or some other physical agent might. Certainly, if a major metabolic abnormality exists (and accumulating evidence makes this ever more probable), therapeutic efforts must be directed at reversing this derangement, whatever its cause.

GENES, ENZYMES, AND THE CENTRAL NERVOUS SYSTEM

The association of mental deficiency with the urinary excretion of phenylpyruvic acid was first reported by Folling in 1934 and soon confirmed by others,[97] although its incidence among institutionalized defectives tends to average 0.64 per cent.[98] The detection of abnormally high amounts of phenylalanine in the body of fluids of phenylketonuries and their failure to respond to the feeding of phenylalanine with the formation of tyrosine led Jervis[99] to the hypothesis that the basic metabolic failure lies in the inability to hydroxylate phenylalanine in the para position.[100] The increased urinary excretion of phenylpyruvic, phenylacetic, and phenyllactic acid was regarded as the end result of the diversion of phenylalanine into an ordinarily minor metabolic pathway. Yet considerable uncertainty existed about the metabolite or metabolites[98] that might account for the central nervous system dysfunction; was it a deficiency state (of phenylalanine or tyrosine) or a toxic state (due to phenylalanine derivatives)?

The inability of the patients to handle phenylalanine led several investigators almost simultaneously to attempt the experiment of feeding phenylalanine-low diets to such patients.[101] Changes in I.Q., in seizures, and in social behavior have been reported to follow this dietary management, at times with striking results, at

others with less impressive but nonetheless promising clinical improvement.[102-104] It would appear that the therapeutic promise is the greater if the diet can be administered at a very early age and it is diligently pursued; the long-term results will of course be known only in the future.

Recent investigations have resulted in exciting leads for the understanding of the basic mechanism of the disorder. Biochemical evidence indicates that the failure of para-hydroxylation of phenylalanine results in its diversion, not only along the metabolic pathway to phenylpyruvic acid, etc., but as well to a second cycle beginning with ortho-hydroxylation.[105] When ortho and meta tyrosines are fed to mice, rats, rabbits, or dogs, central excitatory effects result, which are probably explicable from the finding of the corresponding tyramines in the brains of these animals.[106] (The amounts of tyramines are increased by the simultaneous administration of iproniazid, an amine oxidase inhibitor). Moreover, Mitoma[107] has succeeded in isolating the phenylalanine hydroxylase system which is necessary for the formation of tyrosine in the normal. It consists of Fraction I, found only in liver, and Fraction II, found in all tissues. Mitoma and collaborators[108] have shown that Fraction II is present in normal amounts in ketonuries, whereas Fraction I is absent from liver biopsy specimens of patients but present in normals.[109]

Thus, phenylketonuria emerges as a liver disease, in which a key enzyme necessary for the hydroxylation of phenylalanine to tyrosine is missing. In consequence of this, part of the dietary phenylalanine (60 per cent) is converted into urinary excretion products which enable the clinical detection of the disorder. A second moiety of the ingested amino acid is converted into aberrant tyrosines which may be the responsible agents for the central nervous system dysfunction associated with the metabolic disorder. Dietary management may arrest the production of the abnormal metabolites if the patient can be treated before permanent damage has been produced. The identification of the crucial enzyme system may leave us with the hope that biochemists may yet enable us to supply the patient with the phenylalanine hydroxylase he lacks and thus restore his health on a more physiologic basis.

A second major development lies in the elucidation of the biochemical abnormality underlying congenital galactosemia. The fact that the infant with this disorder shows dramatic clinical improvement when placed on a galactose-free diet has been known since 1935.[110] It is only within the past year that the specific enzymatic deficiency has been established.[111-113] An ingenious series of biochemical investigations have demonstrated that lysed red cells of infants with the disorder lack an enzyme known as uridyl transferase whose function is to catalyze the incorporation of galactose-1-phosphate into a nucleotide to form uridine diphosphogalactose. It is in this form that the galactose is then converted into glucose and enters into the corresponding metabolic cycle. The clear evidence that galactosemia is a heritable disorder indicates a genetic defect which leads to the lack of the enzyme: galactose-1-phosphate uridyl transferase which is absent in cord blood from such infants. Evidence from biochemical studies of mutant microorganisms indicates that a family of related genetic defects may have the same biochemical issue and sug-

gests the need for a careful study of groups of such patients before an assumption that they constitute a homogeneous group is warranted.[114] It is difficult to restrain one's enthusiasm for the elegance of this series of studies which has succeeded in so precisely isolating a heritable enzymatic defect to whose basis a clinical syndrome is so clearly ascribable.

CLINICAL STUDIES

This review has emphasized matters of a fundamental nature in medical psychology; these are the issues that are debated in journals not ordinarily accessible to the pediatrician. It seems only fitting, however, to conclude with at least brief mention of clinical problems under current consideration in the hope of providing appropriate references for those who wish to pursue particular topics.

Until recently, we have had precious little knowledge of the long-term course of children with psychiatric illnesses. However, the Hopkins[115] and Bellevue[116] studies have provided data on the outcome of psychotic children followed into adolescence and early adulthood. I have elsewhere[117] attempted an evaluation of the current status of the diagnosis, course, and treatment of childhood schizophrenia. Follow-up studies at the Pennsylvania Hospital[118] have indicated the rather grim prognosis for children with aggressive behavior disorders. In one of the most important current investigations, O'Neal and Robins[119] are attempting to determine the outcome of 500 children seen diagnostically at a St. Louis guidance clinic in the years 1925-1930. As these results become available, they will have important implications for mental hygiene theory and practice.

The systematic epidemiologic investigations of Pasamanick and associates.[120-125] support the concept of a "continuum of reproductive casualty," extending from fetal and neonatal death at one end of the spectrum, through cerebral palsy, epilepsy, and mental deficiency, to behavior disorders at the other. The clinically important syndrome of specific reading disability has been the subject of two excellent studies[126, 127] which support the notion that there is underlying organic dysfunction in a certain group of these patients. Money[128] and Smith and co-workers[129] have presented data to document the dependence of intellectual growth in severe cretinism upon early adequate therapy. The symptomatology of the child with brain injury has been examined in relation to known principles of central nervous system function.[130] The dynamic origin and the psychotherapeutic management of school phobia, a variant of separation anxiety, has been discussed in several papers[131-134] that should be familiar to the pediatrician.

Considerations of time and space preclude further discussion of other important developments. But perhaps enough has been provided the reader by now to suggest the rapidity and the scope of progress in neuropsychiatry. No longer are we limited to airy speculation without fact or to the plodding accumulation of descriptive statistics; out of the welter of investigative efforts are beginning to emerge the bases for unifying concepts of human behavior. To no medical practitioner are these notions of more importance than to the pediatrician. It is he who can intervene in the earliest

stages of development to promote psychologic health. And, indeed, as modern therapies convert pediatric practice more and more to the care of long-term illness, the handicapping psychologic disorders will tend to pre-empt his time and interest. Psychiatrically competent pediatricians constitute our first line of defense against mental illness.

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Comments on Current Literature

AGENESIS OF THE SPLEEN

CONGENITAL absence of the spleen has been reported in both children and adults. The cases in infants almost invariably have been associated with serious anomalies, such as malformations of the cardiovascular system, partial situs inversus of abdominal viscera with mesenteric anomalies, and abnormalities of the pulmonary system. In the early recorded cases in infants and young children it was the pathologist who recognized this association of anomalies. More recently, however, clinical diagnosis has been possible during the life of the patient. Over the intervening years, a number of reports appeared dealing with cardiac and other anomalies curiously associated with agenesis of the spleen. Polhemus and Schafer,[1] in 1952, reviewed the literature, and pointed out for the first time apparently that such congenital anomalies and absence of the spleen bear a relationship.

The most recent review is that of Biörn I. Ivemark,[2] in a monograph supplement to *Acta Paediatrica* for November, 1955, who collected the cases in the literature from the first case of Martin (1826), and added fourteen cases of his own. In this careful, detailed analysis of cardiac malformations associated with splenic agenesis, Ivemark approaches the classification of cases from the standpoint of organogenesis, and postulates that "the basic lesion of the heart during organogenesis occurred while the spleen should have been in its early formative stage of development."[2] A correlative study pursued by the author included the normal embryology of the cono-truncus and the atrioventricular canal at the time of early splenic organogenesis, and a serial study of the splenic primordia in six human embryos, obtained from the collection of the Karolinska Institute, Stockholm.

In accord with some previous authors, Ivemark believes that congenital absence of the spleen (asplenia) associated with other congenital malformations constitutes a definite pathologic complex and suggests that this complex be called "asplenia, a teratologic syndrome of visceral symmetry." Fourteen new cases are described by this author. The malformed hearts which occurred in association with asplenia displayed a high proportion of atrioventricular anomalies of various types and a high incidence of conotruncus anomalies. All cases showing atrioventricular anomalies showed also malformations of the cono-truncus. In a comment on possible etiology, Ivemark considers these findings the result of developmental arrest of unknown etiology, and states that in no known instance was the mother exposed to rubella, nor was there any family relationship among the fourteen cases presented. There is in the literature, however, a suggestion of familial occurrence. One of the patients described by Polhemus and Schafer[1] was reported to have had an only sibling who died at 11 months of age from cyanotic congenital heart disease, with autopsy findings revealing persistent atrioventricularis communis, multiple accessory spleens, partial transposition of abdominal viscera, and a Meckel's diverticulum. The second child in this family, one of the cases of Polhemus and Schafer, was a female infant who died at a few weeks

of age from combined anomalies almost identical with those of the sibling.

Serious infections occurred in a number of cases described by Ivemark, especially in patients under the age of one year. Meningitis was the most common type of infection. In this connection the author discusses briefly the occurrence of severe infection in the splenectomized patient. A case report by Myerson and Koelle[3] in the *New England Journal of Medicine* (June 14, 1956) is of interest; this report concerns splenic agenesis in an adult, a 36-year-old man, without other anomalies apparently, who experienced frequent infections and recurrent Waterhouse-Friderichsen syndrome. Types of infection included recurrent upper respiratory disease, pneumonia, acute meningitis, with type 22 pneumococcus cultured from both blood and spinal fluid, and repeated urinary tract infections. Pathologic diagnoses at the time of necropsy were given as acute and healed meningitis, bilateral adrenocortical hemorrhage, pneumonia, purulent cystitis, and congenital absence of the spleen.

A recent issue of the *Archives of Disease in Childhood*[4] (April, 1957) carries a report by David Levy from the Pediatric Service of the Rambam Government Hospital in Haifa, Israel, describing the course of a male newborn infant who was transferred to that hospital on the fifth day of life because of cyanosis, and who died on the thirty-first day of life from severe septicemia unresponsive to antibiotic therapy. This child had been born in a private maternity clinic after prolonged labor. The mother was a primipara, primigravida, 22 years of age. She denied any rash or serious illness during the pregnancy. Cyanosis was noted in the newborn infant within twenty-four hours after birth, and on the fifth day of life a systolic murmur was detected over the apex. On admission to the Rambam pediatric service, the infant presented an essentially normal appearance except for the distinct cyanosis seen in the lips, ear lobes, nail beds and skin. The apex beat of the heart was noted on the right side of the sternum in the fourth intercostal space. Heart sounds were clear, and best heard on the right side of the chest. Spleen and liver were not palpable under the costal margin. A radiogram of the abdomen showed normally placed viscera; radiological study of the chest was reported as indicating dextrocardia, confirming the clinical impression. The left lung was shadowed at this time. Examination one week later revealed shadows in both upper lobes. An electrocardiogram on the eighth hospital day indicated sinus tachycardia, and the cardiac diagnosis given at this time was probable tricuspid atresia, trilocular heart. In spite of vigorous therapy, the course continued downhill, and the child died on the thirty-first day of life. About twenty-four hours before death, small fluctuant nodules appeared on the anterior chest wall. Immediately after death one of these was aspirated; on culture, the aspirated pus yielded *Proteus vulgaris* in pure culture.

The necropsy findings, given by the author in some detail, include the following: essential normal position of the abdominal organs; liver asymmetric; spleen entirely absent. In the chest a retrosternal abscess communicated with a subcutaneous abscess through a necrotic zone in the upper part of the sternum. Changes in the lungs were not remarkable. The heart lay in the right hemithorax with apex pointing left; left aortic arch showed normal branching; the ductus arteriosus was obliterated. There was evidence of purulent pericarditis. Septal defects were observed between the auricles and the ventricles; the right atrium was rudimentary, and the right ventricle poorly developed. The tricuspid valve was atretic; the pulmonary veins formed a common trunk which communicated with the superior vena cava, and entered the right atrium. The pulmonary artery arose from the right ventricle; the superior vena cava communicated with the

pulmonary vein in the right lung and with the innominate vein which entered the left atrium. The inferior vena cava entered the right atrium. The aorta arose from the left ventricle, the abdominal aorta descending normally on the left, and the inferior vena cava on the right. Passive congestion of the abdominal viscera was apparent, and there was evidence of septicemia.

Thus the post-mortem diagnosis in this case included, on the one hand, multiple congenital anomalies consisting of malformations of the heart and great vessels, and splenic agenesis, and, on the other hand, various manifestations of widespread sepsis. The author emphasizes the fact that while "the signs and symptoms of septicaemia were readily recognized during life, the symptoms and signs of the heart anomalies were partly misinterpreted and diagnosed only at necropsy."[4]

Apparently possible agenesis of the spleen was not considered during life in this case, a fact which led the author to discuss some of the reported cases of severe infection in asplenia, or following splenectomy. He stresses, as have others, that splenectomy in the infant before the age of 6 months is a more hazardous procedure from the standpoint of susceptibility to infection than in older children, and that "serious infections in a cyanotic infant, even without clear-cut evidence of heart disease, should . . . serve as indications for the search for co-existent asplenia."[4] In a survey of the literature Levy was impressed with certain hematologic findings as a diagnostic aid during life in splenic agenesis. In 1952 Gasser and Willi[5] reported a persistently increased number of erythrocytes showing the Heinz inclusion body in the peripheral blood of two unrelated full-term infants for whom the necropsy diagnosis was almost identical: congenital heart and intestinal malformations with splenic agenesis. Likewise, Bush and Ainger,[6] in 1955, reported a case of congenital anomalies of the heart and viscera in which ante-mortem diagnosis of asplenia was made on the basis of changes in hematologic morphology similar to those observed following splenectomy: "target cells, decreased osmotic fragility, Howell-Johnson bodies, transient normoblastemia, siderocytosis, and leukocytosis."[6] A similar case was described recently by Plowman[7] in a memorandum from the Children's Hospital, Manchester, England. This infant, under close observation from the age of 48 hours to the time of death from gastrointestinal infection at 13 weeks, showed normoblastemia with altered osmotic fragility of red cells. Post-mortem examination revealed cardiac anomalies and malformations of the gastrointestinal tract with complete agenesis of the spleen. While these hematologic findings are not in themselves pathognomonic of splenic agenesis, as Levy points out, the complete hematologic examination advocated by Bush and Ainger in such cases is advisable, especially in a cyanotic infant subject to severe recurrent infections.

The recent reports concerned with infection in splenectomized patients[8] and the current observations that patients with splenic agenesis, either alone or as a part of a more extensive malformation complex, respond poorly in the event of infection serve to emphasize the vital role of the spleen in the defense mechanisms of the body.

RUSSELL J. BLATTNER

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News and Notes

Dr. Laurence R. DeBuys, a well-known New Orleans pediatrician, died at his home June 20, 1957. He was an emeritus member of the American Pediatric Society, and president of the American Academy of Pediatrics from 1936 to 1937.

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Dr. Sybil Jean Schellhase, 2025 Port Chicago Highway, Concord, Calif.

Dr. Jeanette Schulz, 938 Pearl St., Alton, Ill.

Dr. Sigmund Schwarzer, 728 E. 23rd St., San Bernardino, Calif.

Dr. Alfred Loring Skinner, 7705 Sunset Highway, Mercer Island, Wash.

Dr. David W. Smith, 218 Bachman Ave., Los Gatos, Calif.

Dr. Esmond S. Smith, 16100 Ventura Blvd., Encino, Calif.

Dr. Sidney Smith, 601 Cascada Way, Los Angeles 49, Calif.

Dr. Elmer E. Specht, 34 W. 28th Ave., San Mateo, Calif.

Dr. David E. Stanford, 2005 Court St., Redding, Calif.

Dr. Francis Laurance Sult, 611 15th Ave. S., Nampa, Idaho.

Dr. George Ayao Tanbara, No. 30 Tacoma Medical Center, Tacoma 5, Wash.

Dr. Edward A. Thistlewaite, 2 N. Garfield Ave., Alhambra, Calif.

Dr. William H. Tooley, 2320 Channing Way, Berkeley, Calif.

Dr. Edward W. Torello, Jr., 1740 Marco Polo Way, Burlingame, Calif.

Dr. John Cramton Tower, 610 2nd Ave., Anchorage, Alaska.

Dr. Beverly Groat Wagner, 2315 Stockton Blvd., Sacramento, Calif.

Dr. Jacob J. Wiener, St. Albans Naval Hospital, St. Albans, L. I., N. Y.

Dr. Miriam G. Wilson, 2718 N. Beverly Glen Blvd., Los Angeles, Calif.

Dr. Louis Zamvil, 555 Bryon St., Palo Alto, Calif.

The following passed their examination in New Orleans, La., in February, 1957, but were not eligible to receive certificates until July 1, 1957:

Dr. William W. Cleveland, Department of Pediatrics, Jackson Memorial Hospital, Miami, Fla.

Dr. Elwood Brogden Coley, 523 S. Chestnut St., Henderson, N. C.

Dr. Ramiro P. Estrada, 318 N. Santa Rosa St., San Antonio, Texas.
Dr. Richard William Goldsmith, 17 Dickman Ave., Fort Leavenworth, Kan.
Dr. John Francis Ivey, 1645 San Marco Blvd., Jacksonville, Fla.
Dr. John C. Kramer, 1547 S. Lewis St., Tulsa, Okla.
Dr. William Locke Moore, 1006 Professional Village, Greensboro, N. C.
Dr. Eugene B. Orgeron, 541-543 9th Ave., Port Arthur, Texas.
Dr. Hilda de Martinez Polo, 400 Ponce de Leon Ave., Hato Rey, Puerto Rico.
Dr. Jack Herbert Rubinstein, 130 E. Shields St., Cincinnati, Ohio.
Dr. Roy Godfrey Young, Jr., 917 17th St., S., Apt. B., Birmingham, Ala.

Special Foreign Certificates:

Dr. Pelino V. Barnes, P. O. Box 3609, Manila, Philippines.
Dr. Maret Champion, 36 Victoria Rd., Bellevue Hill, Sydney, New South Wales, Australia.
Dr. Krishnakant Hiralal Desai, North Carolina State Sanatorium, McCain, N. C.
Dr. Abdul Sahib Hashim, c/o C. W. McDill, 916 Woodlawn Ave., Springfield, Ohio.
Dr. Nirmal Kumar Mitra, Children's Mercy Hospital, Kansas City 6, Mo.
Dr. Garuda Venkata, Rama Row, c/o Mercy Hospital, N. Calvert St., Baltimore, Md.
Dr. Antonio Dennis Reis, 22 Aleman St., Quezon City, Philippines.
Dr. Maarten Smit Sibinga, 172 Ludlow St., N. Y. 2, N. Y.
Dr. Jose Maria Teran, 3a. Ave. N.O.-No. 505, Managua, Nicaragua.
Dr. Constantino L. Valido, The Jewish Hospital Association, Cincinnati 29, Ohio.
Dr. Mohsen Ziai, Thorndike Laboratory, Boston City Hospital, Boston, Mass.
Dr. Audrey E. Evans, 300 Longwood Ave., Boston, Mass.

Dr. Nathan J. Smith has been appointed the first "Alfred D. Daniels" professor of pediatrics at the University of Wisconsin Medical School at Madison, Wisconsin. He will be chairman of the department and pediatrician-in-chief of the University Hospital. He was formerly associate professor of pediatrics at the University of California at Los Angeles. The Daniels professorship was established last year in memory of Dr. Daniels by his son.

Applications for the residency from July 1, 1958, to June 30, 1959, in Pediatric Oncology at Memorial Center for Cancer and Allied Diseases in New York will be received up to Nov. 1, 1957. This residency is approved for partial credit by the American Board of Pediatrics and is limited to the neoplastic diseases of children. Salary: $3,600 annually plus maintenance. For application forms and information write: Director, Pediatric Service, Memorial Center for Cancer and Allied Diseases, 444 East 68th St., New York 21, N. Y.

The **Skin and Cancer Hospital-Temple University Medical Center**, Philadelphia, announces the second annual course in *Pediatric Dermatology* to be held in Philadelphia, Oct. 14 to 19, 1957. Detailed information can be obtained from Dr. Henry H. Perlman, Pediatric Dermatology Committee, Skin and Cancer Hospital, 804 Pine St., Philadelphia 7, Pa.

The 1957 annual convention of the **National Society for Crippled Children and Adults**—the Easter Seal Society—will be held Oct. 31 to Nov. 2, 1957, in Chicago at the Palmer House. Dr. James B. Johnson, Newark, Ohio, is chairman of the 1957 convention.

The **American Psychosomatic Society** will hold its Fifteenth Annual Meeting at the Netherland Hilton in Cincinnati on March 29 and 30, 1958. The program committee would like to receive titles and abstracts of papers for consideration for the program no later than Nov. 15, 1957. The time allotted for presentation of each paper will be twenty minutes. Abstracts of the papers in octuplicate should be submitted for the program committee's consideration and sent to the Chairman, Dr. Theodore Lidz, 551 Madison Ave., New York 22, N. Y.

The 1958 **Eastern States Health Education Conference** of The New York Academy of Medicine will be held April 24 and 25, 1958, at the Academy, 2 East 103rd St., New York City.

The **American Association for Cleft Palate Rehabilitation** will be holding its 16th annual convention at the St. Francis Hotel in San Francisco on April 24 to 26, 1958. The Association is composed of medical, dental, and paramedical specialists who are interested in the rehabilitation of persons with cleft lips and palates.

The New York Academy of Medicine will hold a postgraduate week (replacing the Graduate Fortnight of former years), Oct. 7 to 11, 1957. The general subject is *Research Contributions to Clinical Practice.*

Evening Lectures—8:30 P.M.

October 7

The Structure and Development of Viruses Revealed by the Electron Microscope by Councilman Morgan, College of Physicians and Surgeons, Columbia University.

Implications of 60 Newly Recognized Viruses of Man by Robert J. Huebner, National Institutes of Health, Bethesda, Md.

Clinical Aspects of Viral Diseases by Robert Ward, New York University College of Medicine.

October 8

Aspects of Carbohydrate and Phosphate Metabolism in Diabetes by William C. Stadie, University of Pennsylvania School of Medicine.

Fat Metabolism in Diabetes by Vincent P. Dole, The Rockefeller Institute for Medical Research.

Modern Aspects of the Diabetes Problem by Garfield G. Duncan, University of Pennsylvania School of Medicine.

October 9

Disturbances of Amino Acid Metabolism by L. Emmett Holt, Jr., New York University College of Medicine.

Connective Tissues in Medicine and Surgery by Jerome Gross, Harvard Medical School.

Current Concepts of the Homoplasty Enigma by Richard B. Stark, College of Physicians and Surgeons, Columbia University.

October 10

Potassium and the Kidney by Gilbert H. Mudge, The Johns Hopkins University School of Medicine.

Renal Tubular Dysfunction in Congestive Heart Failure by Louis Leiter, College of Physicians and Surgeons, Columbia University.

Renal Excretion of Uric Acid in Gout: Modification by Uricosuric Agents in Treatment by Alexander B. Gutman, College of Physicians and Surgeons, Columbia University.

October 11

Current Views on the Biochemistry and Physiology of Myocardial Contraction by H. Mead Cavert, University of Minnesota Medical School.

Physiology of Hypothermia by James E. Eckenhoff, University of Pennsylvania Schools of Medicine.

The Present Status and the Probable Direction of Future Developments in Open Cardiotomy in the Correction of Cardiac Defects by John H. Gibbon, Jr., The Jefferson Medical College.

Panel Meetings—3:30 P.M.

Oct. 7: Thyroid Disease. Chairman: Rulon W. Rawson, Memorial Center for Cancer and Allied Diseases.

Oct. 8: Adrenal Gland and Adrenal Tumors. Chairman: Joseph W. Jailer, College of Physicians and Surgeons, Columbia University.

Oct. 9: Modern Aspects of Hematology. Chairman: Irving M. London, Albert Einstein College of Medicine, Yeshiva University.

Oct. 10: Practical Application of Radioactive Metals. Chairman: Lee E. Farr, Brookhaven National Laboratory Hospital.

Oct. 11: Blood Proteins. Chairman: Henry G. Kunkel, The Rockefeller Institute for Medical Research.

A registration fee is required for non-Fellows of the Academy. Medical Officers of the Armed Services, in uniform, will be admitted without charge. Interns and Residents will be admitted without charge, provided they present letters from their chiefs of service. All inquiries and requests for registration should be addressed to: Secretary, Postgraduate Week, The New York Academy of Medicine, 2 East 103rd St., New York 29, N. Y.

Books

Orthopaedic Surgery in Infancy and Childhood. Albert Barnett Ferguson, Jr., Baltimore, 1957, Williams & Wilkins Co., 508 pages. Price $15.00.

The author of the above book has dealt well with a subject which had to be sandwiched in between already well-established textbooks on orthopedic surgery, textbooks on fractures, including fractures in children, and Campbell's two-volume *Operative Orthopaedics*. Pediatricians have long hoped for a book of this nature, and in this book they will find the subjects divided into the various regions of the body. The book begins with the foot and then follow, in turn, the knee, the hip, the spine, the upper extremity, and the neck. There is an excellent chapter on Affections of Bone, Affections of the Nerves and of the Muscles. Finally there is a short chapter on Malignant Tumors of Bone in Children. Each of the above sections is well covered, and credit is given to various methods of treating different affections, just as it is found in *American Orthopedics*. The author's handling of his material reflects his excellent training at the Boston Childrens and Massachusetts General Hospitals. The author wisely credits his teachers with many of the thoughts, procedures, and treatments outlined in the book.

This reviewer finds himself in virtually complete agreement with everything handled in the text, except for some minor criticisms. The author has used the term "apophysis" instead of "epiphysis" when speaking of the epiphysis of the os calcis, iliac crest, and the tibial tubercle. Repeated usage of the term "apophysis" for "epiphysis," by orthopedic surgeons, has given the term the standing of correctness; however, anatomists insist the term should be limited to the joints of the spine only. Therefore, in order to keep confusion to a minimum, it is my opinion that the term "apophysis" for the epiphysis of the os calcis, the tibial tubercle, the crest of the ilium, et cetera, should be abandoned. Unfortunately, typographical errors in some of the names in the references, and occasional typographical errors in the text, give it an appearance of having been hurriedly done. Although this detracts from the over-all splendidness of this book, I am sure that in future revisions these will be corrected.

The author and his collaborators have performed a distinct service in this publication, and I am sure that students of all ages will benefit from owning this very useful book.

R. T. O.

Children's Eye Problems. Emanuel Krimsky, New York and London, 1956, Grune & Stratton, Inc., 175 pages.

In the preface it is stated that "the aim of this book is to provide the pediatrician and the general practitioner with a practical, usable guide to the understanding of children's eye problems." A careful reading of the text forces the conclusion that this aim has not been achieved. The book is poorly organized, and the trend of thought is frequently difficult to follow. The style is awkward, the grammar unbelievably bad. Although a great many disease entities are mentioned, most are discussed so briefly that nothing will be gained by those experienced in the field and little more by those who are not.

The book contains misleading half-truths, misconceptions, and many frank errors; moreover, some of the author's recommendations are patently dangerous. As of today it would seem ill advised to suggest that the etiology of retrolental fibroplasia is as yet unknown (p. 4). The superior tarsus is not cartilaginous (p. 34). Styes and pinkeye should not be treated with systemic penicillin as a primary procedure (pp. 35, 42). Tubular vision does not occur in glaucoma (p. 59). It is not true that "the eyeball maintains its spherical shape largely because

of a thick, transparent, jelly-like substance that fills the vitreous cavity behind the crystalline lens'' (p. 62). Few ophthalmologists would agree that ''digital palpation of the eyeball to measure tenseness is often preferred to instrument methods which yield unsatisfactory readings,'' and that ''examination of these young infants under general anesthesia is often unsatisfactory'' (p. 88). Niemann-Pick disease is not the juvenile form of Tay-Sachs disease (p. 116).

There are more serious misstatements. On page 75, it is stated that ''in traumatic retinal detachment eventual spontaneous recovery may take place if the child is kept quiet for a few weeks.'' Although not strictly untrue, this statement might be extremely misleading to someone inexperienced in the field. On page 93, it is stated that ''treatment is usually inadvisable in congenital cross eye and in many cases of paralytic strabismus which often clear up spontaneously.''

But most dangerous of all are the author's recommendations concerning steroid therapy in virus infections of the cornea. He suggests ''prescribing eyedrops which might counteract the offending virus, such as cortisone.'' These drops are to be used ''usually every hour, and continued for a few days. . . . Failure of cortisone to help the corneal condition often suggests herpes simplex'' (p. 67). Most ophthalmologists have seen the tragic results of steroid-treated corneal infections. It is well known that by the time the diagnosis is made by the method described above, irreparable damage has already been done by the steroids.

This carelessly prepared book cannot be recommended for the pediatrician.

L. T. P., JR.

The Fight for Fluoridation. Donald R. McNeil, New York, 1957, Oxford University Press, 251 pages. Price, $5.00.

The story of the cause of mottled enamel and the application of this knowledge to the prevention of the disease, dental caries, is told beautifully in this small book. The author has written a narrative with the romantic interest of a historical novel and at the same time has omitted little necessary to a good understanding of the history of this development.

The sociologic implications and the discussions for and against fluoridation are presented comprehensively. The difficult task of composing an over-all picture of such a complex and highly scientific problem in terms that would appeal to the lay reader or to scientists, in fields other than this one, has been handled satisfactorily. The reader seldom loses interest in the narrative.

As the story of this public health measure continues to unfold, it is thought that recommendation of this book for general reading would be apropos, as the interest in the problem on the part of the laity is ever increasing. At the present time this is the best-written and the most authoritative short book on the subject.

Water Fluoridation: Facts, Not Myths. Louis I. Dublin, 1957, Public Affairs Pamphlets, 22 East 38th St., New York 16, N. Y., 28 pages. Price 25 cents (quantity rates lower).

This is an excellent pamphlet for physicians to use who live in communities where fluoridation is still a matter of controversy. After a foreword by Dr. Benjamin Spock, Dr. Louis I. Dublin, public health authority and consultant to the Institute of Life Insurance, has marshaled the facts regarding the value of fluoridation in preventing dental caries and in its complete safety. While the facts are well known to the medical profession, and fluoridation is supported by many national associations, such as the American Medical Association, American Dental Association, and the Academy of Pediatrics, there is a vociferous opposition group with little respect for facts. The text is clear and straightforward and intended for nonmedical readers. The illustrations are clever and to the point. The pamphlet is published by the Public Affairs Committee, a nonprofit organization, which has brought out many pamphlets on health and social problems. Pediatricians who are so vitally concerned with preventive medicine, living in cities where fluoridation is still a matter of controversy, will find this pamphlet excellent educational material for the parents of the children in their practice.

B. S. V.

Editor's Column

MEDICINE IN RED CHINA

WITH our lack of knowledge of what is going on in "Red" China —recently emphasized by the controversy between the Press and the State Department in Washington over passports—a recent report* on some medical developments is of unusual interest, especially since several medical schools were established in China by American physicians over half a century ago, and later the Rockefeller Foundation spent large sums of money developing the medical school at Peking in an effort to bring modern medicine to China. Many Chinese physicians have studied in the United States and have friendships with American physicians.

The report, entitled "The Activities of the Chinese Medical Association and Its Future Tasks," by Fu Lien-Chang, is most revealing of what has been happening to Chinese medicine under Communist rule. The point that is stressed throughout is the bringing together of the traditional-style physicians with those trained in modern medicine. ("Traditional-style" doctors are commonly referred to as "herb" doctors but not in the report.) The report is even quite apologetic of the Association for paying insufficient attention to the matter "in spite of an appeal from the Central Committee of the Party to study the ancient medical heritage of our country and put it at the service of the people." The Medical Association is stated to have 15,059 members, including 1,037 traditional-style doctors who were admitted since the Association's doors were opened to them in 1954. Despite this, "little was done to utilize fully the service of traditional doctors or in research in traditional medicine." "A change finally came about upon repeated instructions from the Central Committee of the Party. . . ." "Now that a large number of hospitals throughout the country are inviting traditional-style doctors to participate in their work, cooperation has become closer as regards both the study and practice of medicine." Obviously the Chinese doctors trained in modern medicine received stern orders direct from party headquarters.

A number of statements under the heading "Shortcomings" are quite illuminating. The cooperation is stated to be beginning "but has not yet, by a long way, attained *what is required of us in this respect*" (italics ours). "The attitude of indifference, or even disparagement, towards our traditional-style doctors and medical heritage has been criticized, but evidently not severely enough." "No clear decisions have yet been made as to the

*Summing up report presented at the Tenth General Conference of the Chinese Medical Association, Peking, July 23 to 29, 1956.

Reprinted in the *Indian Journal of Pediatrics* 23: 426, 1956.

most effective method of learning from traditional doctors or the best order in which Chinese medical books should be studied."

The report goes on to state that the Peking branch of the Association has compiled a catalog of books on Chinese medicine in the five big libraries in Peking and that these activities are being "coordinated with the movement to learn from Chinese medicine." "Before liberation there were in our country the 'English,' 'German,' 'American,' and 'Japanese' cliques in medicine which existed to 'contend' for their own fame, benefit, and position. We oppose such schools. . . ." "To learn from the medical heritage of our country is an important part of our struggle on the scientific front." "We must continue to criticize disparagement of our traditional medicine and contempt for traditional-style doctors, for such behaviour obstructs cooperation between the two schools."

In the report some account is given of the "academic activities" of the Association, which has forty-three local branches. Societies in special fields have been organized. We learn that in 1954 the Society of Obstetrics and Gynecology conducted an analysis of 33,000 cases of ovarian and uterine tumors collected from thirteen hospitals in nine cities, and that the "Society of Tuberculosis has adopted the Soviet classification of tuberculosis" (whatever this may be). The Society of Otorhinolaryngology has been examining the possibilities of using acupuncture in the treatment of ear, nose, and throat conditions. The Association publishes sixteen medical journals, with ninety-five issues a year. One of these is published in English. "What is specially worth mentioning is that the contents of most of the journals have been strengthened as regards our traditional Chinese medicine."

The need for international cooperation is stressed. It is stated that medical delegations came to China from France, Japan, and the Argentine. In 1955 a friendly agreement was signed with the Japanese delegation to exchange specialists to give lectures. A delegation from the Association attended the "World Congress of Doctors for the Study of Present-Day Living Conditions" held in Vienna in 1953 and on their way back visited Leningrad, Moscow, Prague, and Bruno.

A "twelve-year plan" for medical research is now being formulated, with attention directed primarily to the prevention and cure of the prevalent diseases, arranging and systematizing the theories of Chinese medicine, inquiry into new drugs, research in labor hygiene, and improvement of the environmental hygiene and the nutrition of the people.

Soviet medical influence is seemingly dominant, but with some scientific reservations by the Association. "There have been striking developments during the past few years in learning from the advanced medical science of the Soviet Union. Enthusiasm for the study of Pavlov's theories have increased greatly since the Ninth General Conference (1952) and in both medical research and clinical work Pavlov's views are becoming the basis of medical thought." "From now on while still concentrating on learning from Soviet medicine, we must at the same time study and learn from the

medical achievements and contributions of all other countries. We should learn not only from the Peoples Democracies, but also from the capitalist countries." "Pavlov's ideas are undoubtedly the most advanced in medical theories, but we should not promote them to the exclusion of other theories and ideas."

From the report we gather that the Chinese physician trained in modern medicine is not having an easy time. While it is seemingly necessary to obey political dictation in a Communist country, it apparently has not been easy to carry out the Party edict to cooperate with and learn from the traditional-style doctor. A second difficulty seems to lie in a conflict between his scientific integrity and the acceptance of the materialistic medical philosophy of Pavlov, which dominates Soviet medicine, as the final supreme authority.

These direct quotations from the report give an idea of what seemingly is happening to medicine in Communist China. Apparently in 1953, under orders from the Central Committee of the Party, a decree was issued, directing that the traditional-style doctors and those trained in modern western medicine must cooperate and learn from one another. For this reason the Chinese Medical Association opened its doors to the traditional-style doctor in 1954. Just what political or social reason brought about this decree is not stated. Obviously the "cooperation" has been slow, and the Association not only is being prodded by the Party authorities, but, from the tenor of the report, is also on the defensive. That cooperation in "learning from each other" is slow is not surprising when the differences in their education and philosophy are taken into consideration. It is obvious that medicine in China under the Communist regime is facing backward rather than forward. It is an example of what can happen when science is dictated to and dominated by politics.

No comment or explanation is made as to just why the *Indian Journal of Pediatrics* saw fit to reprint this report from the *Chinese Medical Journal*.